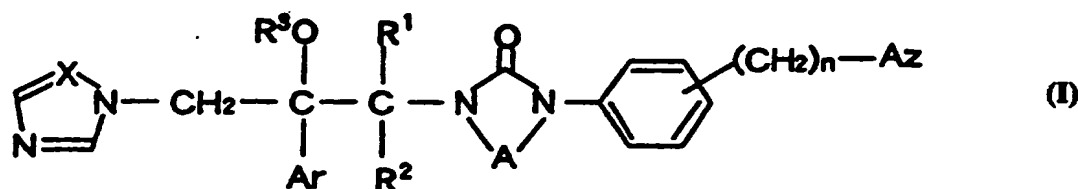




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07D 403/14, A61K 31/41</b>	<b>A1</b>	(11) International Publication Number: <b>WO 96/25410</b> (43) International Publication Date: 22 August 1996 (22.08.96)
<p>(21) International Application Number: PCT/JP96/00325</p> <p>(22) International Filing Date: 15 February 1996 (15.02.96)</p> <p>(30) Priority Data: 7/29579 17 February 1995 (17.02.95) JP 7/285318 1 November 1995 (01.11.95) JP</p> <p>(71) Applicant (for all designated States except US): TAKEDA CHEMICAL INDUSTRIES, LTD. [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka 541 (JP).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): ITOH, Katsumi [JP/JP]; 18-12, Kofudai 6-chome, Toyono-cho, Toyono-gun, Osaka 563-01 (JP). OKONOGI, Kenji [JP/JP]; 5-20-101, Wakayamadai 1-chome, Shimamoto-cho, Mishima-gun, Osaka 618 (JP). TASAKA, Akihiro [JP/JP]; 9-20-102, Yamadahigashi 2-chome, Suita-shi, Osaka 565 (JP).</p> <p>(74) Agent: NOGAWA, Shintaro; Quarter-1 Building, 5-1-3 Nishitenma, Kita-ku, Osaka-shi, Osaka 530 (JP).</p>	<p>(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, KE, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report.</p>	

(54) Title: AZOLE COMPOUNDS, THEIR PRODUCTION AND USE



## (57) Abstract

The present invention provides an azole compound represented by formula (I), wherein Ar is an optionally substituted phenyl group; R<sup>1</sup> and R<sup>2</sup>, the same or different, are a hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> may combine together to form a lower alkylene group; R<sup>3</sup> is a hydrogen atom or an acyl group; X is a nitrogen atom or a methine group; A is Y-Z (Y and Z, the same or different, are a nitrogen atom or a methine group optionally substituted with a lower alkyl group) or an ethylene group optionally substituted with a lower alkyl group; n is an integer from 0 to 2; and Az is an optionally substituted azolyl group, or its salt, which is useful for a prevention and therapy of a fungal infection of a mammal as an antifungal agent.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

## DESCRIPTION

## Azole Compounds, Their Production and Use

## TECHNICAL FIELD

The present invention relates to azole compounds useful as antifungal therapeutic agents, methods for producing them and use thereof.

## BACKGROUND ART

A variety of azole compounds have been reported exhibiting antifungal activity (see, for example, EP0122056A1, EP0332387A1, EP0122693A1 and EP0567982A).

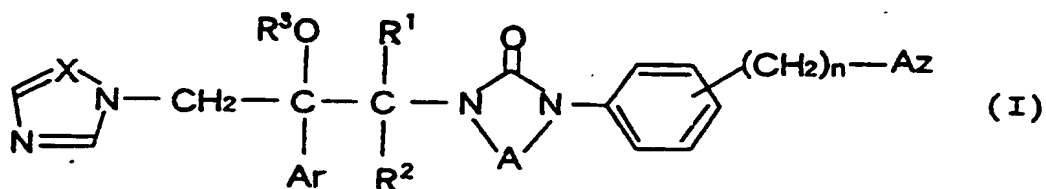
None of these azole compounds, however, is satisfactory as a pharmaceutical agent in terms of its antifungal activity, antifungal spectrum, side effect and in vivo pharmacokinetics.

There has been a demand for a safer compound which exhibits better absorption in vivo and higher antifungal activity as an antifungal therapeutic agent.

## DISCLOSURE OF INVENTION

The present invention provides

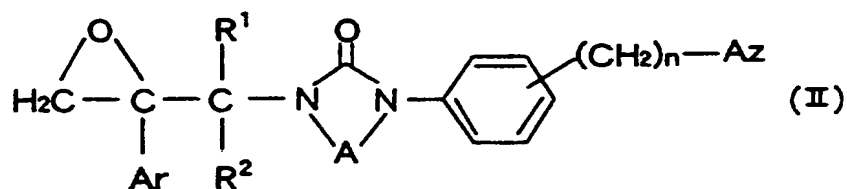
(1) a compound represented by the formula (I):



wherein Ar is an optionally substituted phenyl group;  
 $R^1$  and  $R^2$ , the same or different, are a hydrogen atom or a lower alkyl group, or  $R^1$  and  $R^2$  may combine together to form a lower alkylene group;  $R^3$  is a hydrogen atom or an acyl group; X is a nitrogen atom or a methine group; A is Y=Z (Y and Z, the same or different, are a nitrogen atom or a methine group optionally substituted with a lower alkyl group) or an ethylene group optionally substituted with a lower alkyl group; n is an integer from 0 to 2; and Az is an optionally substituted azolyl group, or a salt thereof,

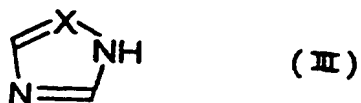
(2) a process for preparing a compound of the formula (I) as defined in claim 1 or a salt thereof which comprises

(i) reacting a compound represented by the formula (II):



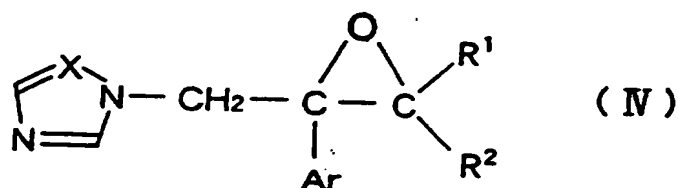
wherein the symbols have the same meanings as defined above; or a salt thereof

with a compound represented by the formula (III):



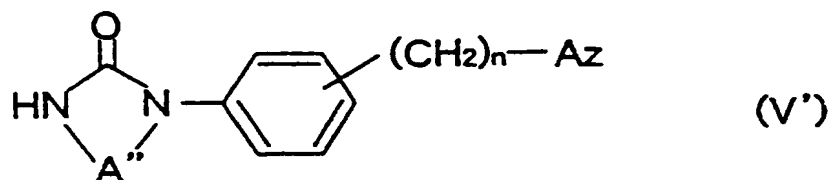
wherein the symbols have the same meanings as defined above; or a salt thereof, and, if necessary, followed by an acylation;

(ii) reacting a compound represented by the formula (IV):



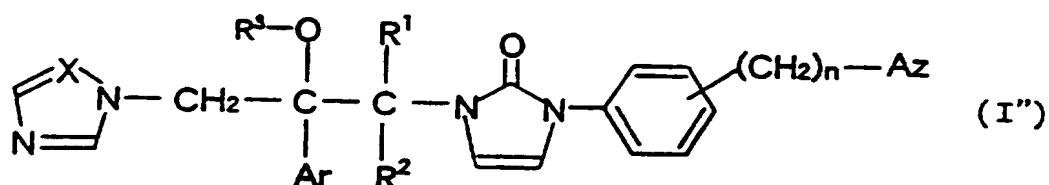
wherein the symbols have the same meanings as defined above; or a salt thereof

with a compound represented by the formula (V'):



wherein A'' is -N=CH-, -CH=N- or -CH=CH-; the symbols have the same meanings as defined above; or a salt thereof, and, if necessary, followed by an acylation; or

(iii) reducing a compound represented by the formula (I'')



wherein the symbols have the same meanings as defined above; or a salt thereof, and, if necessary, followed by an acyla-

tion,

(3) a pharmaceutical composition to be an antifungal preparation containing a compound represented by the above formula (I) or a salt thereof.

Examples of the substituents for "optionally substituted phenyl group" represented by Ar in the formula (I) include halogen atoms (e.g., fluorine, chlorine, bromine and iodine), lower (C<sub>1-4</sub>) haloalkyl, lower (C<sub>1-4</sub>) haloalkoxy, lower (C<sub>1-4</sub>) alkylsulfonyl, lower (C<sub>1-4</sub>) haloalkylsulfonyl and the like. Preferably, the substituent is halogen atoms (e.g., fluorine, chlorine, bromine and iodine), and more preferably it is fluorine. The number of the substituents is preferably from one to three, more preferably from one to two.

Examples of Ar include halophenyl, lower (C<sub>1-4</sub>) haloalkylphenyl, lower (C<sub>1-4</sub>) haloalkoxyphenyl, lower (C<sub>1-4</sub>) alkylsulfonylphenyl, lower (C<sub>1-4</sub>) haloalkylsulfonylphenyl and the like.

Examples of the halophenyl groups include 2,4-difluorophenyl, 2,4-dichlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 2-chlorophenyl, 2-fluorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, 2,4,6-trifluorophenyl, 4-bromophenyl and the like.

Examples of the lower (C<sub>1-4</sub>) haloalkylphenyl groups include 4-trifluoromethylphenyl group and the like.

Examples of the lower ( $C_{1-4}$ ) haloalkoxyphenyl groups include 4-trifluoromethoxyphenyl, 4-(1,1,2,2-tetrafluoroethoxy)phenyl, 4-(2,2,2-trifluoroethoxy)phenyl, 4-(2,2,3,3-tetrafluoropropoxy)phenyl, 4-(2,2,3,3,3-pentafluoropropoxy)phenyl and the like.

Examples of the lower ( $C_{1-4}$ ) alkylsulfonylphenyl groups include 4-methanesulfonylphenyl and the like.

Examples of the lower ( $C_{1-4}$ ) haloalkylsulfonylphenyl groups include 4-(2,2,2-trifluoroethanesulfonyl)phenyl, 4-(2,2,3,3-tetrafluoropropanesulfonyl)phenyl, 4-(2,2,3,3,3-pentafluoropropanesulfonyl)phenyl and the like.

Specific examples of the phenyl groups of Ar are phenyl groups substituted with one to two halogen atoms such as 2,4-difluorophenyl, 2,4-dichlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 2-chlorophenyl, 2-fluorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, 4-bromophenyl and the like, among which phenyl groups substituted with one or two fluorine atoms such as 4-fluorophenyl, 2-fluorophenyl and 2,4-difluorophenyl are more preferable and 2-fluorophenyl and 2,4-difluorophenyl are most preferable.

Examples of the lower alkyl groups represented by  $R^1$  or  $R^2$  in the formula (I) include straight or branched  $C_{1-4}$  alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl and the like, among which methyl is more preferable. It is particularly preferable that both of  $R^1$  and  $R^2$  are hydrogen atoms or methyl

groups, or one of  $R^1$  and  $R^2$  is a hydrogen atom and the other is a methyl group.

Examples of the lower alkylene groups formed by the combination of  $R^1$  and  $R^2$  include straight lower ( $C_{2-4}$ ) alkylene groups such as ethylene, propylene, butylene and the like, among which ethylene is preferred.

Among them, it is preferable that one of  $R^1$  and  $R^2$  is a hydrogen atom and the other is a  $C_{1-4}$  alkyl group such as a methyl group and the like.

Examples of the acyl groups represented by  $R^3$  in the formula (I) include acyl groups derived from organic carboxylic acids such as alkanoyl, preferably  $C_{1-7}$  alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, hexanoyl and heptanoyl), more preferably  $C_{1-3}$  alkanoyl; arylcarbonyl, preferably  $C_{7-15}$  arylcarbonyl (e.g., benzoyl and naphthalenecarbonyl), more preferably  $C_{7-11}$  arylcarbonyl group; alkoxycarbonyl, preferably  $C_{2-7}$  alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl and tert-butoxycarbonyl), more preferably  $C_{2-4}$  alkoxycarbonyl; aryloxy carbonyl, preferably  $C_{7-15}$  aryloxy carbonyl (e.g., phenoxycarbonyl), more preferably  $C_{7-11}$  aryloxy carbonyl; aralkylcarbonyl group, preferably  $C_{8-20}$  aralkylcarbonyl (e.g., benzylcarbonyl, phenethylcarbonyl, phenylpropylcarbonyl and naphthylethylcarbonyl), more preferably



C<sub>8-14</sub> aralkylcarbonyl; and the like.

Preferably, the above acyl groups are those being capable of hydrolyzing in vivo. Examples thereof are formyl, acetyl, benzoyl, benzylcarbonyl and the like. Preferred R<sup>3</sup> is a hydrogen atom.

X in the general formula (I) is preferably a nitrogen atom.

Examples of the lower alkyl groups for "a methine group optionally substituted by a lower alkyl group" represented by Y or Z when A is Y=Z in the formula (I) include straight or branched C<sub>1-4</sub> alkyl groups (methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl), among which methyl is preferred.

Examples for the methine group optionally substituted with a lower alkyl group represented by Y or Z include methine, ethylidyne (-C(CH<sub>3</sub>)=), propylidyne (-C(CH<sub>2</sub>CH<sub>3</sub>)=), butylidyne (-C(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)=) and the like, among which methine, ethylidyne and the like are preferable, and methine and the like are more preferable.

It is preferable that one of Y and Z is a nitrogen atom and the other is methine; that both are methine; that both are nitrogen atoms; and one is a nitrogen atom and the other is ethylidyne. It is particularly preferable that one of Y and Z is a nitrogen atom and the other is methine or both of Y and Z are methine.

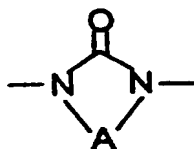
When A is "an ethylene group optionally substituted

with a lower alkyl group" in the formula (I), examples of the lower alkyl groups include straight or branched C<sub>1-4</sub> alkyl groups (methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl), among which methyl, ethyl and the like are preferable, and methyl and the like are more preferable.

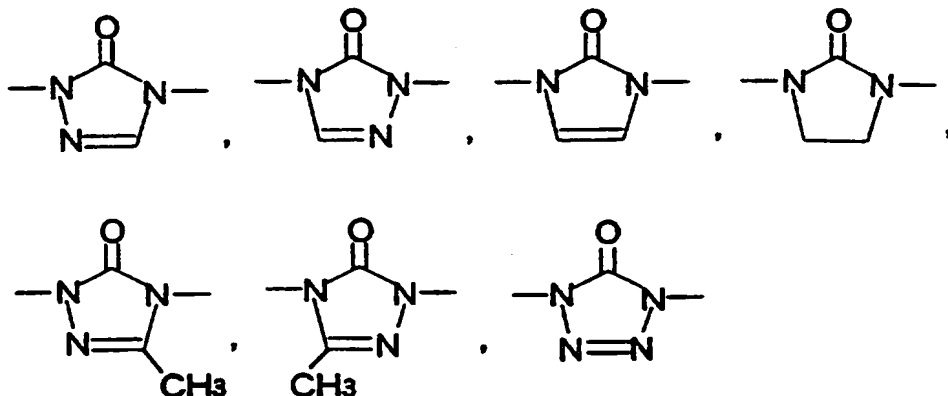
Examples of the ethylene groups optionally substituted with a lower alkyl group represented by A include ethylene, 1-methylethylene, 1,1-dimethylethylene, 1,2-dimethylethylene, 1-ethylethylene, 1,2-diethylethylene and the like, among which ethylene and the like are preferred.

Specific examples of A are -N=CH-, -CH=N-, -CH=CH-, -N=N-, -N=C(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)=N-, -CH<sub>2</sub>-CH<sub>2</sub>- and the like, among which -N=CH-, -CH=N-, -CH=CH-, -CH<sub>2</sub>-CH<sub>2</sub>- and the like are preferred.

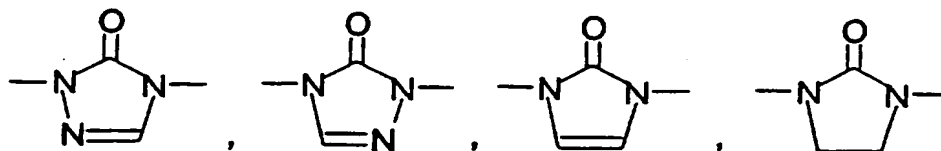
In the formula (I), the groups represented by



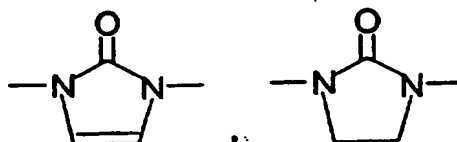
are preferably



and the like, more preferably



and the like, still more preferably



and the like.

The integer from 0 to 2 represented by n is preferably 0 or 1, more preferably 0.

Examples of the azolyl groups for "an optionally substituted azolyl group" represented by Az in the formula (I) include five-membered aromatic heterocyclic groups containing one to four nitrogen atoms as ring-constituent atoms, which may further contain a hetero atom selected from sulfur or oxygen as a ring-constituent atom, such as pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, furazanyl, 1,3,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,4-thiadiazolyl and the like.

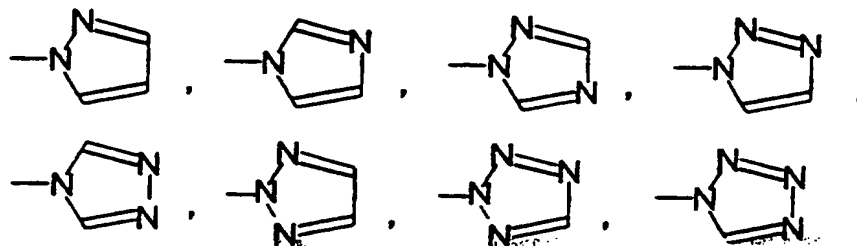
In particular, the azolyl groups are preferably pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl and the like, more preferably 1H-pyrazol-1-yl, 1H-imidazol-1-yl, 1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-2-yl, 1H-1,2,4-triazol-1-yl, 4H-1,2,4-triazol-4-yl, 1H-tetrazol-1-yl, 2H-tetrazol-2-yl and the like, and further more pref-

erably 1H-pyrazol-1-yl, 1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-2-yl, 1H-1,2,4-triazol-1-yl, 1H-tetrazol-1-yl, 2H-tetrazol-2-yl and the like.

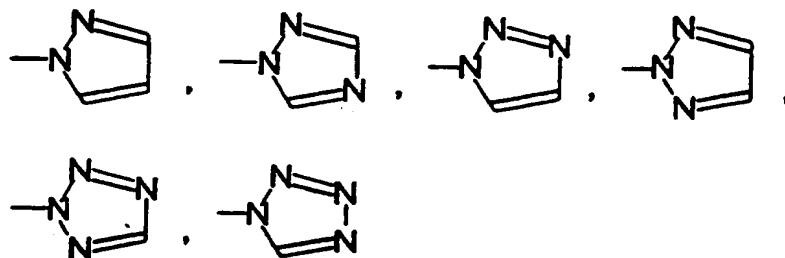
Examples of the substituents for "an optionally substituted azoly group" represented by the above Az include hydroxyl group, optionally esterified carboxyl group (e.g., carboxyl, C<sub>1-6</sub> alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl and butoxycarbonyl), nitro group, amino group, acylamino group (e.g., C<sub>1-10</sub> alkanoylamino such as acetylamino, propionylamino and butyrylamino), mono-C<sub>1-10</sub> or di-C<sub>1-10</sub> alkylamino group (e.g., methylamino, dimethylamino, diethylamino and dibutylamino), C<sub>1-6</sub> alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, sec-butyl, pentyl and hexyl), C<sub>1-6</sub> alkoxy group (e.g., methoxy, ethoxy and butoxy), halogen atom (e.g., fluorine, chlorine and bromine), C<sub>1-6</sub> haloalkyl group (e.g., trifluoromethyl, dichloromethyl, 2,2,2-trifluoroethyl and 2,2,3,3-tetrafluoropropyl), C<sub>1-6</sub> haloalkoxy group (e.g., trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,3-pentafluoropropoxy, 2,2,3,3,4,4,5,5-octafluoropentoxy and 2-fluoroethoxy), oxo group, thioxo group, mercapto group, C<sub>1-6</sub> alkylthio group (e.g., methylthio, ethylthio and butylthio), C<sub>1-6</sub> alkylsulfonyl group (e.g., methanesulfonyl, ethanesulfonyl and butanesulfonyl), C<sub>1-10</sub> alkanoyl group (e.g., acetyl, formyl,

propionyl and butyl), phenyl group, C<sub>1-6</sub> alkylphenyl group (e.g., p-tolyl, mesityl and p-cumenyl), C<sub>1-6</sub> alkoxyphenyl group (e.g., 4-methoxyphenyl and 4-isopropoxyphenyl), halo-phenyl group (e.g., 4-chlorophenyl and 4-fluorophenyl, 2,4,-difluorophenyl), C<sub>1-6</sub> haloalkylphenyl group (e.g., 4-trifluoromethylphenyl), C<sub>1-6</sub> haloalkoxyphenyl group [e.g., 4-trifluoromethoxyphenyl, 4-(2,2,3,3-tetrafluoropropoxy)-phenyl and 4-(1,1,2,2-tetrafluoroethoxy)phenyl] and the like. These substituents may be substituted on the ring-constituent carbon and/or nitrogen atom(s) of the azolyl group and the number of the substituents is preferably one or two.

Specifically, Az are preferably diazolyl, triazolyl and tetrazolyl such as

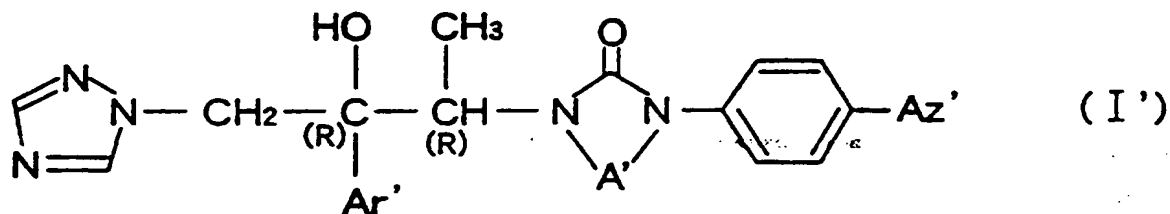


and the like, more preferably



and the like.

A preferred example of the compound (I) is a compound represented by the formula (I')



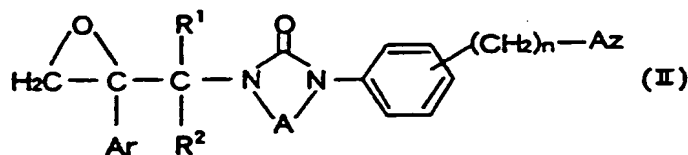
(wherein Ar' is a monofluorophenyl (e.g., 2-fluorophenyl) or difluorophenyl (e.g., 2,4-difluorophenyl) group; A' is -N=CH-, -CH=CH- or CH<sub>2</sub>-CH<sub>2</sub>-; and Az' is an azolyl group selected from the group consisting of a diazolyl, triazolyl, tetrazolyl, thiazolyl or oxazolyl which are optionally substituted with one or two substituents selected from the group consisting of an oxo group, a C<sub>1-6</sub> alkyl group (e.g., methyl, ethyl, n-propyl, iso-propyl), a C<sub>1-6</sub> haloalkyl group (e.g., trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,3,3-tetrafluoropropyl) and a C<sub>1-6</sub> haloalkyloxyphenyl group (e.g., 4-trifluoromethoxyphenyl, 4-(2,2,3,3-tetrafluoropropoxyphenyl, 4-(1,1,2,2-tetrafluoroethoxyphenyl)) or a salt thereof. In the formula (I'), A' is preferably -CH<sub>2</sub>-CH<sub>2</sub>-, and Az' is preferably a triazolyl group and a tetrazolyl group.

The compound represented by the formula (I), (I') may be used as a salt thereof. Examples of such salts are pharmacologically acceptable salts such as inorganic acid salts (e.g., hydrochloride, hydrobromide, sulfate, nitrate

and phosphate), organic acid salts (e.g., acetate, tartrate, citrate, fumarate, maleate, toluenesulfonate and methanesulfonate). When carboxyl group is included in the formula (I) as a substituent, it may be an alkali metal (sodium, potassium and the like) salt.

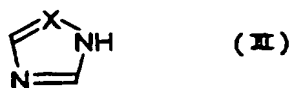
The compounds represented by the formula (I) or a salt thereof (hereinafter abbreviated as the compound of the present invention) have two or more stereoisomers thereof because of having one or more asymmetric carbon atom in their molecule. It should be understood that any of such stereoisomers as well as a mixture thereof is within a scope of the present invention. Among those, when  $R^1$  is hydrogen and  $R^2$  is methyl, both the carbon atom to which the optionally substituted phenyl group represented by Ar is bonded and the carbon atom to which  $R^2$  is bonded are preferred to be in (R)-configuration.

The compound of the present invention can be produced by, for example, reacting a compound represented by the formula (II):



(wherein the symbols have the same meanings as defined above) or a salt thereof

with a compound represented by the formula (III):



(wherein the symbols have the same meanings as defined above) or a salt thereof. This reaction provides a compound of the present invention in which  $R^3$  is a hydrogen atom.

The reaction can be carried out in a solvent which does not inhibit the reaction. Examples of the solvents are water, ketones (e.g., acetone), sulfoxides (e.g., dimethyl sulfoxide), ethers (e.g., diethyl ether, tetrahydrofuran and dioxane), nitriles (e.g., acetonitrile), aromatic hydrocarbons (e.g., benzene, toluene and xylene), halogenated hydrocarbons (e.g., dichloromethane, chloroform and 1,2-dichloroethane), esters (e.g., ethyl acetate), amides (e.g., dimethylformamide, acetamide, dimethylacetamide and 1-methyl-2-pyrrolidinone), ureylenes (e.g., 1,3-dimethyl-2-imidazolidinone) and the like. These solvents may be used either singly or as a mixture of two or more solvents in a suitable mixing ratio.

Further, the reaction is preferably carried out in the presence of a base such as alkali metal hydroxides (e.g., lithium hydroxide, potassium hydroxide and sodium hydroxide), alkali metal hydrides (e.g., potassium hydride and sodium hydride), alkali metal carbonates (e.g., lithium carbonate, sodium bicarbonate, cesium carbonate, potassium



carbonate and sodium carbonate), organic acid salts (e.g., sodium acetate), alkali metal alcoholates (e.g., sodium methylate, potassium tert-butyrate and sodium tert-butyrate), tetrabutylammonium fluoride, bis(tri-n-butylstannyl)oxide and the like.

Alternatively, the desired compound can also be prepared by the reaction in the above solvent using a metal salt (e.g., alkali metal salt such as sodium and potassium salt) of the compound (III) instead of the compound (III).

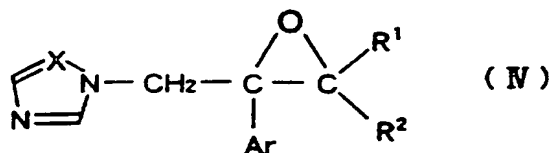
The amount of the base used is usually about 0.01 to at 100 equivalents, preferably about 0.1 to about 50 equivalents per equivalent of the compound of formula (III) or a salt thereof.

The amount of the compound (III) or a salt thereof is about 1 to about 100 equivalents, preferably about 1 to about 50 equivalents per equivalent of the compound of formula (II) or a salt thereof.

The reaction temperature is not especially limited, but usually within the range of about 0 to about 150°C, preferably about 10 to about 120°C.

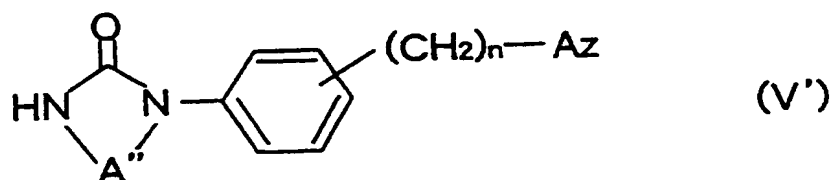
The reaction time is usually within the range of about several minutes to tens of hours (e.g., from five minutes to fifty hours).

In another embodiment, the compound of the present invention can also be prepared by, for example, reacting a compound represented by the formula (IV):

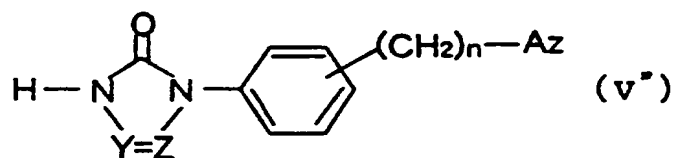


(wherein the symbols have the same meanings as defined above) or a salt thereof

with a compound represented by the formula (V'):



(wherein A" is -N=CH-, -CH=N- or -CH=CH-, the other symbols have the same meanings as defined above) or a salt thereof. The compound of the formula (V') may be a compound represented by the formula (V''):



(wherein the symbols have the same meanings as defined above) or a salt thereof. This reaction provides a compound of the present invention which A is Y=Z and R<sup>3</sup> is hydrogen.

The reaction is usually carried out in a solvent which does not inhibit the reaction. Examples of the solvents are water, ketones (e.g., acetone), sulfoxides (e.g., dimethyl sulfoxide), ethers (e.g., diethyl ether, tetrahydrofuran and dioxane), nitriles (e.g., acetonitrile), aromatic hydrocar-

bons (e.g., benzene, toluene and xylene), halogenated hydrocarbons (e.g., dichloromethane, chloroform and 1,2-dichloroethane), esters (e.g., ethyl acetate), amides (e.g., dimethylformamide, acetamide, dimethylacetamide and 1-methyl-2-pyrrolidinone), ureylenes (e.g., 1,3-dimethyl-2-imidazolidinone) and the like. These solvents may be used either singly or as a mixture of two or more solvents in a suitable mixing ratio.

Further, the reaction is preferably carried out in the presence of a base such as alkali metal hydroxides (e.g., lithium hydroxide, potassium hydroxide, sodium hydroxide), alkali metal hydrides (e.g., potassium hydride and sodium hydride), alkali metal carbonates (e.g., lithium carbonate, sodium bicarbonate, cesium carbonate, potassium carbonate and sodium carbonate), organic acid salts (e.g., sodium acetate), alkali metal alcoholates (e.g., sodium methylate, potassium tert-butyrate and sodium tert-butyrate), tetrabutylammonium fluoride, bis(tri-n-butylstannyl)oxide and the like.

Alternatively the desired compound can also be prepared by the reaction in the above solvent using a metal salt (e.g., alkali metal salt such as sodium and potassium salt) of the compound (V') or (V'') instead of the compound (V') or (V'').

The amount of the base used is usually about 0.01 to

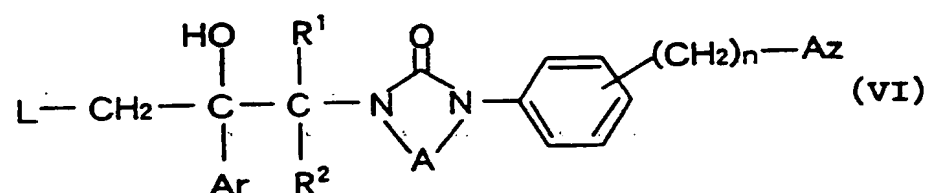
about 100 equivalents, preferably about 0.1 to about 50 equivalents per equivalent of the compound of formula (V') or a salt thereof or (V'') or a salt thereof.

The amount of compound (V') or (V'') or a salt thereof is about 1 to about 100 equivalents, preferably about 1 to about 50 equivalents per equivalent of the compound of formula (IV) or a salt thereof.

The reaction temperature is not especially limited, but usually within the range of about 0 to about 150°C, preferably about 10 to about 120°C.

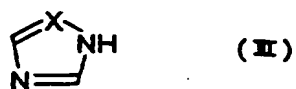
The reaction time is usually within the range of about several minutes to tens of hours (e.g., from five minutes to fifty hours).

According to another embodiment, the compound of the present invention can be prepared by, for example, reacting a compound represented by the formula (VI):



{wherein L is a leaving group [e.g., halogen atom (e.g., chlorine, bromine and iodine) or R<sup>4</sup>SO<sub>3</sub> (wherein R<sup>4</sup> is lower (C<sub>1-4</sub>) alkyl group or optionally substituted phenyl group)] and the other symbols have the same meaning as defined above} or a salt thereof

with a compound represented by the formula (III):



(wherein the symbols have the same meaning as defined above) or a salt thereof. This reaction provides a compound of the formula (I) in which  $R^3$  is hydrogen.

Examples of the  $C_{1-4}$  lower alkyl group represented by  $R^4$  are methyl, ethyl, propyl, butyl and tert-butyl.

Examples of the optionally substituted phenyl group are the same as those of the optionally substituted phenyl group represented by Ar.

The reaction is usually carried out in a solvent which does not inhibit the reaction. Examples of the solvents are water, ketones (e.g., acetone), sulfoxides (e.g., dimethyl sulfoxide), ethers (e.g., diethyl ether, tetrahydrofuran and dioxane), nitriles (e.g., acetonitrile), aromatic hydrocarbons (e.g., benzene, toluene and xylene), halogenated hydrocarbons (e.g., dichloromethane, chloroform and 1,2-dichloroethane), esters (e.g., ethyl acetate), amides (e.g., dimethylformamide, acetamide, dimethylacetamide and 1-methyl-2-pyrrolidinone), ureylenes (e.g., 1,3-dimethyl-2-imidazolidinone) and the like. These solvents may be used either singly or as a mixture of two or more solvents in a suitable mixing ratio.

Further, the reaction is preferably carried out in the presence of a base such as alkali metal hydroxides (e.g., lithium hydroxide, potassium hydroxide and sodium

hydroxide), alkali metal hydrides (e.g., potassium hydride and sodium hydride), alkali metal carbonates (e.g., lithium carbonate, sodium bicarbonate, cesium carbonate, potassium carbonate and sodium carbonate), organic acid salts (e.g., sodium acetate), alkali metal alcoholates (e.g., sodium methylate, potassium tert-butyrate and sodium tert-butyrate), tetrabutylammonium fluoride, bis(tri-n-butylstannyl)oxide and the like.

Alternatively the desired compound can be prepared by the reaction in the above solvent using a metal salt (e.g., alkali metal salt such as sodium and potassium salt) of the compound (III) instead of the compound (III).

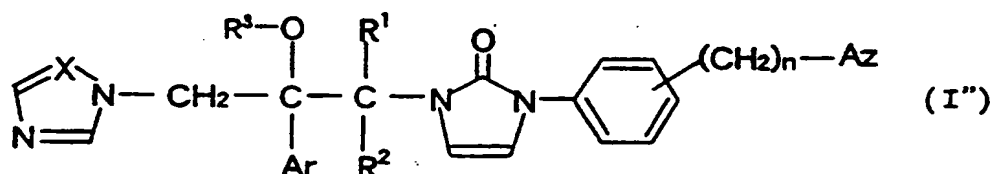
The amount of the base used is usually within the range of about 2 to about 100 equivalents, preferably about 2 to about 50 equivalents per equivalent of the compound of formula (III) or a salt thereof.

The amount of the compound (III) or a salt thereof is usually within the range of about 1 to about 100 equivalents, preferably about 1 to about 50 equivalents per equivalent of the compound of formula (VI) or a salt thereof.

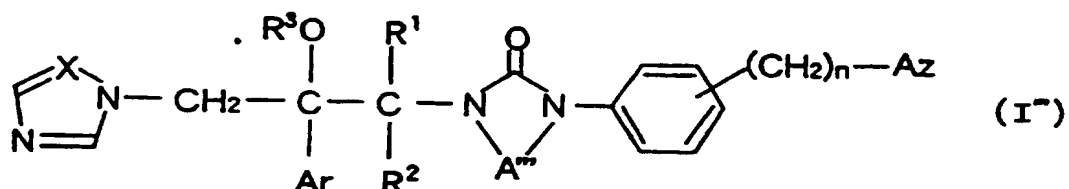
The reaction temperature is not especially limited, but usually about 0 to about 150°C, preferably about 10 to about 120°C.

The reaction time is about tens of minutes to tens of hours (e.g., from thirty minutes to fifty hours).

The compound of the present invention wherein A is an ethylene group optionally substituted with a lower alkyl or salt thereof can be prepared by, for example, subjecting to a catalytic reduction a compound of the formula (I''):



(wherein the symbols have the same meaning as defined above) or a salt thereof, or the compound of the formula (I) wherein Y and Z are methine groups optionally substituted with lower alkyl (i.e., a compound (I''')):



(wherein A''' is a vinylene group optionally substituted with lower alkyl group and the other symbols have the same meanings as defined above) or a salt thereof.

The above-mentioned reaction is usually carried out in the presence of a single or mixed solvent(s) such as water and organic solvents which do not inhibit the reaction such as ketones (e.g., acetone and methylethyl ketone), alcohols (e.g., methanol, ethanol, propanol, isopropyl alcohol and butanol), esters (e.g., ethyl acetate), hydrocarbons (e.g.,

benzene, toluene, hexane and xylene), organic carboxylic acids (e.g., acetic acid and propionic acid) and the like. The reaction is usually carried out in the presence of catalyst. A suitable metal catalyst such as palladium-carbon is used as the catalyst. The reduction reaction is carried out at a pressure from atmospheric pressure up to about 150kg/cm<sup>2</sup> at a temperature from room temperature up to about 100°C.

Examples of the salts of the above starting compounds (II), (IV), (VI), (I'') and (I''') are the same as those of the compounds (I).

When a compound or a salt thereof of the present invention wherein R<sup>3</sup> is a hydrogen atom is obtained in the above reactions, the obtained compound or a salt thereof can be converted into by the conventional method to provide a compound of the formula (I) wherein R<sup>3</sup> is an acyl group, by treating it with an appropriate acylating agent of R<sup>3</sup>L<sup>1</sup> [wherein R<sup>3</sup> is an aliphatic or aromatic carboxylic acid residue (e.g., acetyl, propionyl, butyl, ethoxycarbonyl, benzoyl, substituted benzoyl) and L<sup>1</sup> is group to be removed (e.g., a halogen atom such as chlorine, bromine and the like, an active ester)] in accordance with the conventional method.

The above-mentioned reaction is usually carried out in the presence or absence of a solvent which does not inhibit the reaction. Examples of such solvents are water, ketones



such as acetone, sulfoxides such as dimethyl sulfoxide, ethers such as diethyl ether, tetrahydrofuran and dioxane, nitriles such as acetonitrile, aromatic hydrocarbons such as benzen, toluene and xylene, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane, esters such as ethyl acetate, amides such as dimethylformamide, acetamide, dimethylacetamide, ureylenes such as 1,3-dimethyl-2-imidazolidinone, and the like. Also a base (e.g., dimethylaminopyridine, pyridine, pyrroline and triethylamine) may be added to the reaction system for accelaration of the reaction. The amount of the base used is usually about 1 to about 100 equivalents per equivalent of the compound of formula (I) or a salt thereof.

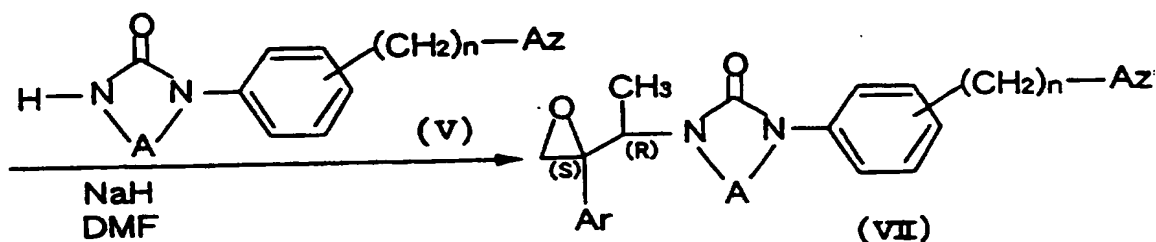
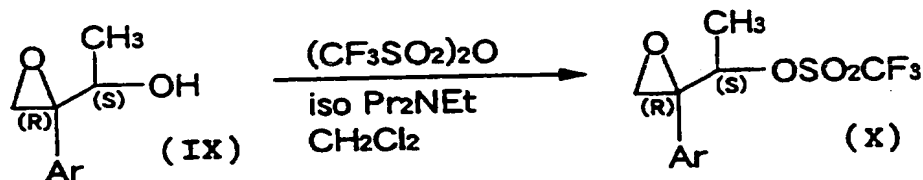
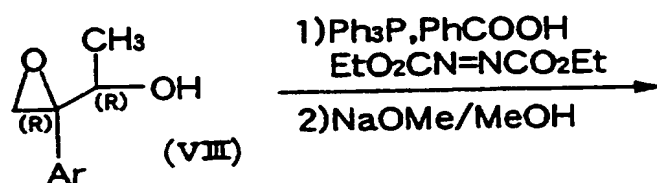
The compound of the present invention obtained as above can be isolated and purified from the reaction mixture by a known procedure per se such as extraction, concentration, neutralization, filtration, recrystallization, column chromatography, thin layer chromatography and the like.

The compound of the present invention may have at least two stereoisomers as mentioned above. Such a stereoisomer can be separately prepared if desired. For example, a single isomer can be obtained by the above reaction using each single isomer of the starting compounds (II), (IV), (VI), (I'') and (I''') or salts thereof. Alternatively, when the obtained product is a mixture of two or more isomers,

they can be separated into each isomer by the conventional separating method such as a method for producing a salt with an optically-active acid (e.g., camphorsulfonic acid and tartaric acid), various types of chromatographies, fractional recrystallization and the like.

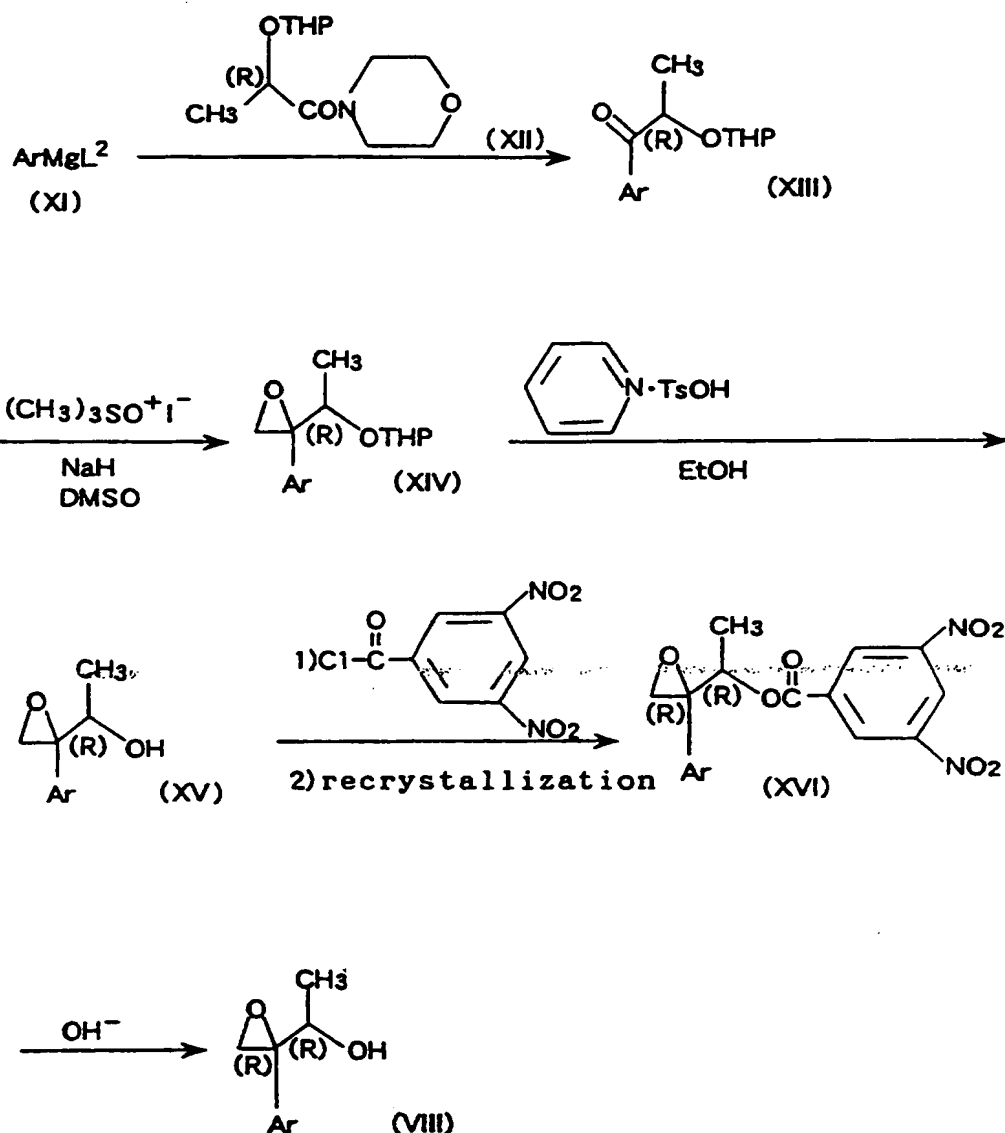
The salt of the compound of the present invention can be prepared by a known method per se such as adding the aforesaid inorganic or organic acid to the compound (I).

The starting compound (II) or a salt thereof in the present invention wherein  $R^1$  is hydrogen,  $R^2$  is methyl, the carbon atom to which Ar is bonded is an (S)-configuration and the carbon atom to which  $R^2$  is bonded is an (R)-configuration [i.e., a compound (VII) or a salt thereof] can be prepared, for example, by a method represented by the following reaction scheme:



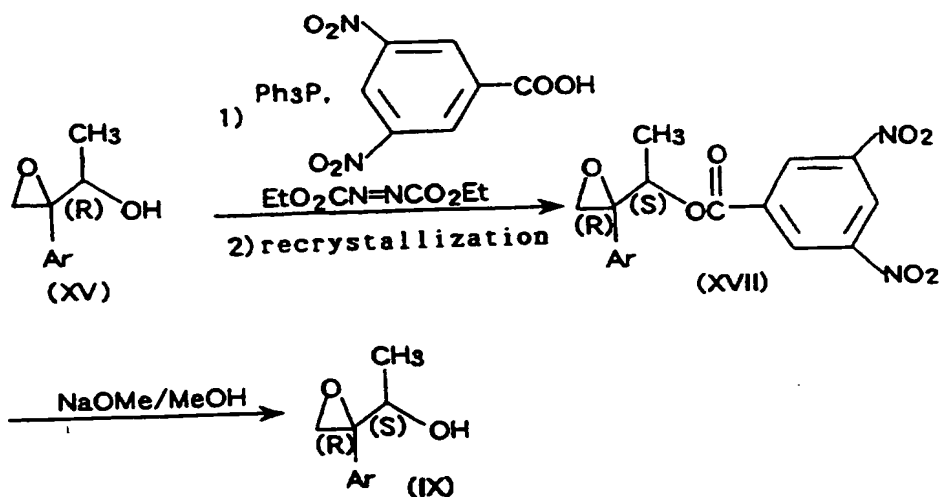
(wherein Me is methyl, Et is ethyl, Pr is propyl, Ph is phenyl, (R) and (S) denote the respectively symbolized configurations of the carbon atoms, DMF is dimethylformamide, and the other symbols have the same meanings as defined above).

The starting compound (VIII) in the reaction can be prepared, for example, by a method represented by the following reaction scheme:



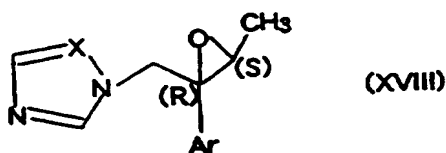
[wherein THP is tetrahydropyranyl group, Ts is p-toluenesulfonyl group,  $L^2$  is a halogen atom (e.g., chlorine, bromine, iodine), DMSO is dimethylsulfoxide, and the other symbols have the same meanings as defined above].

The intermediate compound (IX) can be synthesized, for example, by a method represented by the following reaction scheme:



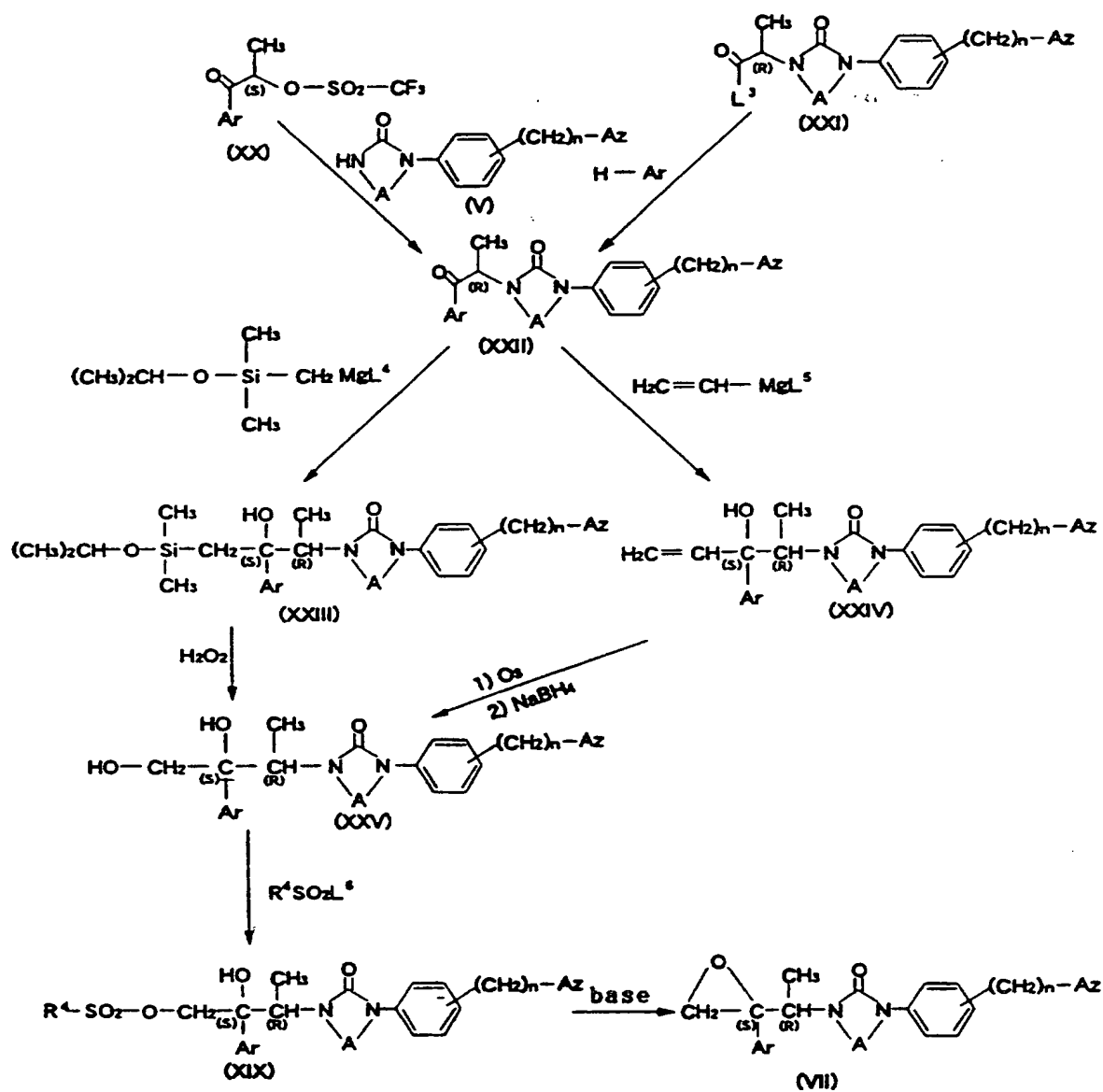
(wherein the symbols have the same meanings as defined above).

The starting compound (IV) in the present invention wherein  $R^1$  is a hydrogen atom,  $R^2$  is a methyl group, the carbon atom to which Ar is bonded is in an (R)-configuration and the carbon atom to which  $R^2$  is bonded is in an (S)-configuration [i.e., a compound (XVIII)]:



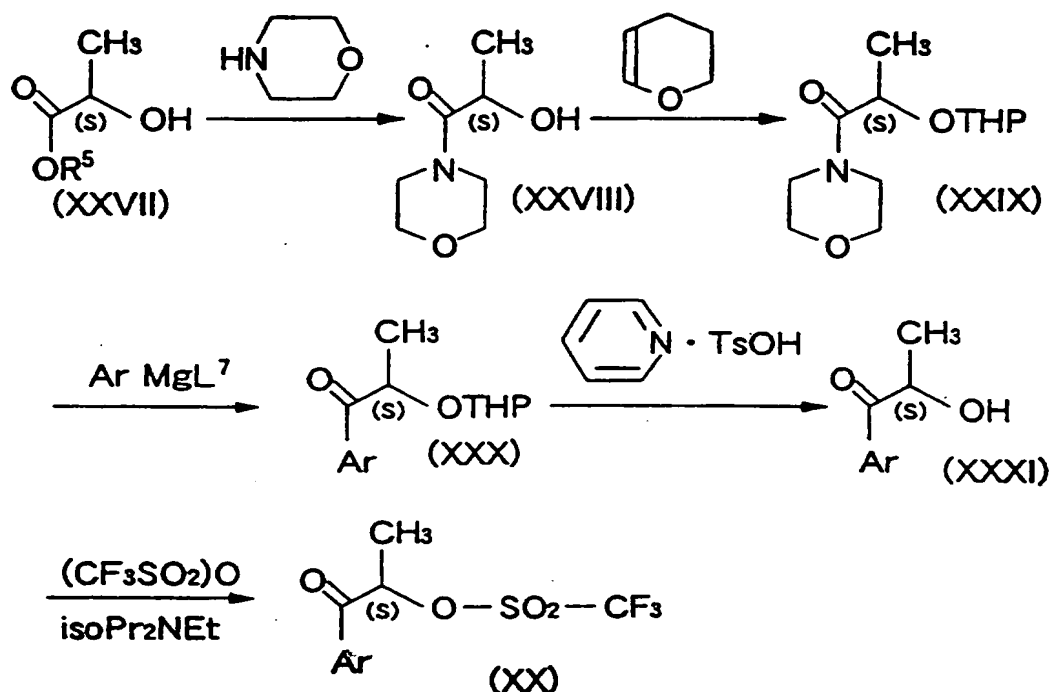
(wherein the symbols have the same meanings as defined above) can be synthesized, for example, by methods described in EP0421210A, EP0548553A or EP0567982A or by a method based thereon.

The starting compound (VI) or a salt thereof in the present invention wherein  $R^1$  is a hydrogen atom,  $R^2$  is a methyl group, the carbon atom to which Ar is bonded in (S)-configuration, the carbon atom to which  $R^2$  is bonded in (R)-configuration, and L is a leaving group represented by  $R^4SO_3$  (wherein  $R^4$  has the same meaning as mentioned above) [i.e., a compound (XIX) or a salt thereof], and the starting compound (II) or a salt thereof in the present invention wherein  $R^1$  is a hydrogen atom,  $R^2$  is a methyl group, the carbon atom to which Ar is bonded in (S)-configuration and the carbon atom to which  $R^2$  is bonded in (R)-configuration [i.e., a compound (VII) or a salt thereof] can be prepared, for example, by a method represented by the following reaction scheme:



[wherein each of  $L^3$ ,  $L^4$ ,  $L^5$  and  $L^6$  is a halogen atom (e.g., chlorine, bromine, iodine) and the other symbols have the same meanings as defined above].

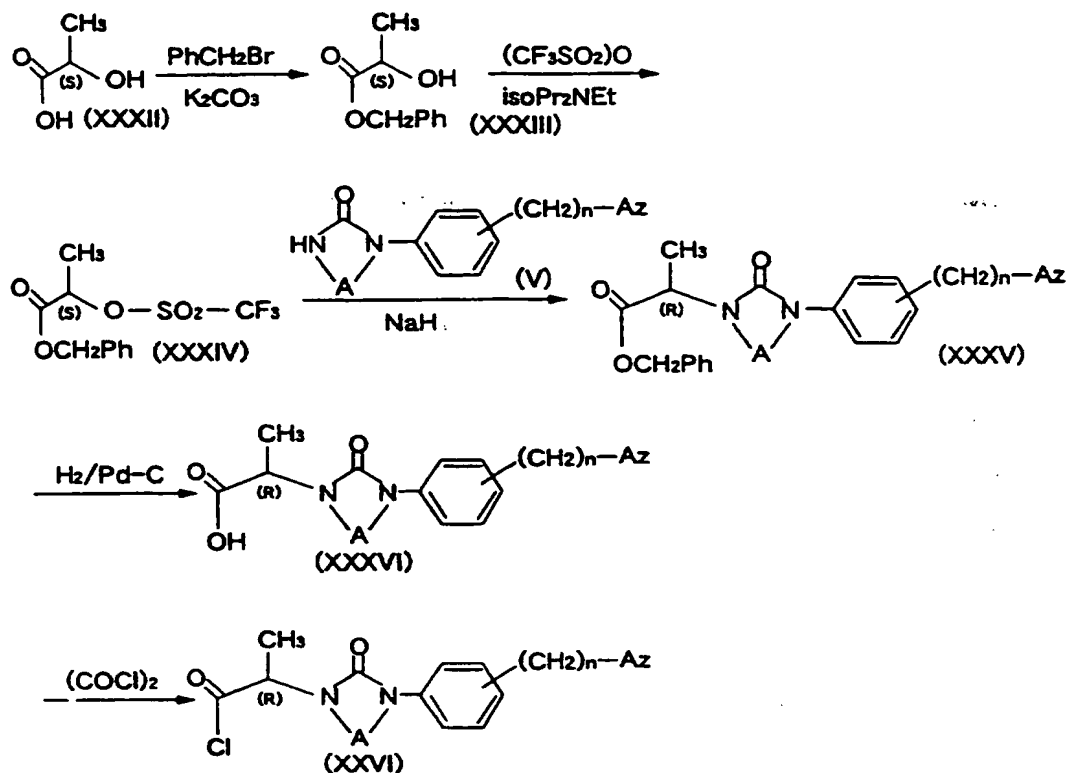
The starting compound (XX) or a salt thereof and the starting compound (XXI) or a salt thereof in the above reaction wherein  $L^3$  is a chlorine atom [i.e., a compound (XXVI) or a salt thereof] can be each prepared, for example, by a method represented by the following reactions scheme:



[wherein  $R^5$  is a lower alkyl group,  $L^7$  is a halogen atom (e.g., chlorine, bromine, iodine) and the other symbols have the same meanings as defined above].

A synthesizing method for a compound (XXXI) or a salt thereof in which Ar is 2, 4-difluorophenyl as mentioned in the above reaction scheme is described in Japanese Patent

Laid-Open No. HEI 5(1993)-230038.



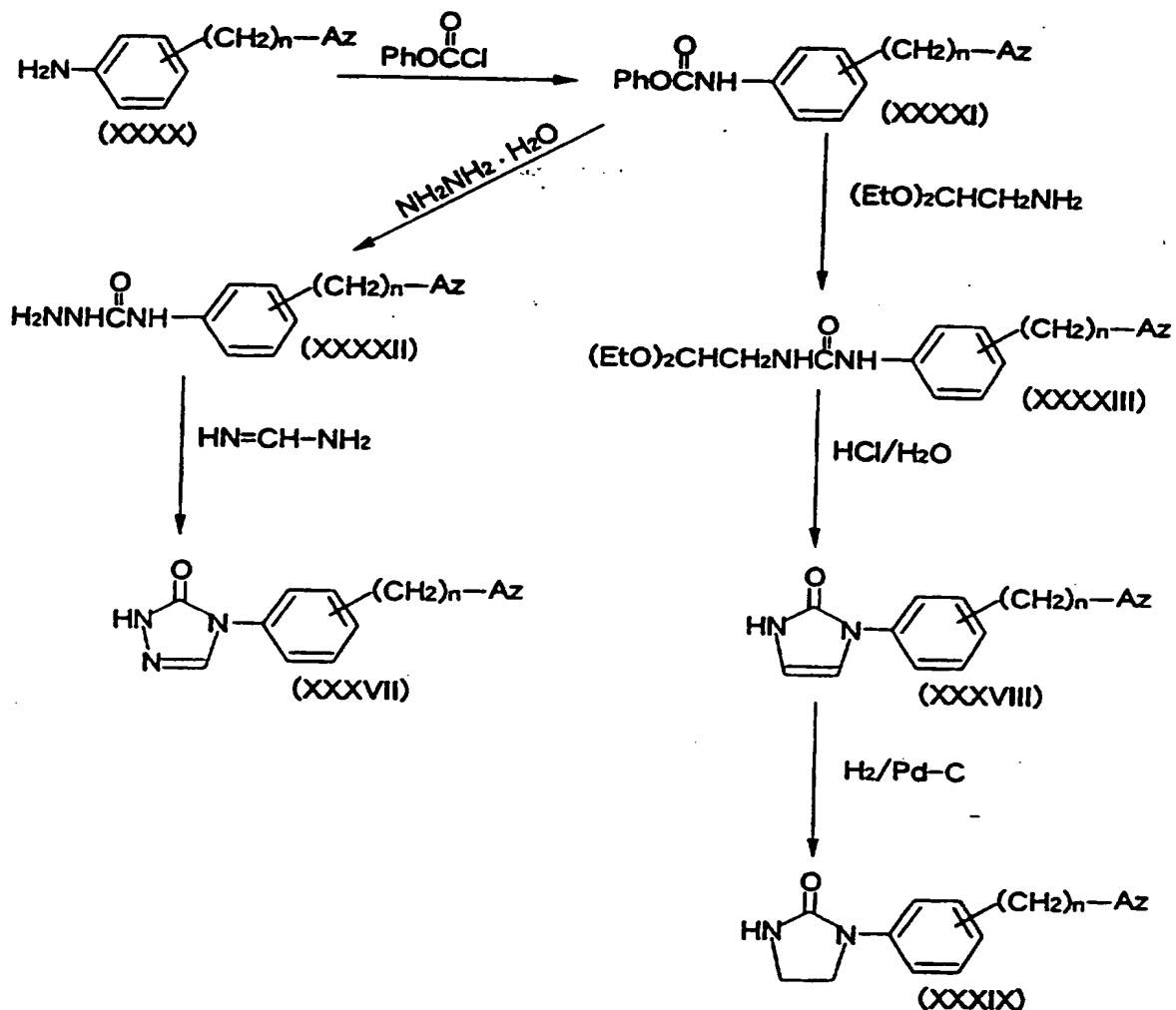
(wherein  $\text{H}_2/\text{Pd-C}$  denotes a catalytic reduction using palladium-carbon catalyst and the other symbols have the same meanings as defined above).

A compound (XXI) or a salt thereof wherein  $\text{L}^3$  is a halogen atom except chlorine can be prepared using the corresponding halogenating agent [e.g.,  $(\text{COBr})_2$ ,  $\text{PBr}_3$ ] instead of  $(\text{COCl})_2$  in a similar way to the above reaction.

The starting compounds (V) or a salt thereof in the present invention wherein A is  $-\text{N}=\text{CH}-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{CH}_2-\text{CH}_2-$  [i.e., compounds (XXXVII), (XXXVIII) and (XXXIX) or salts thereof respectively] can be prepared, for example, by the

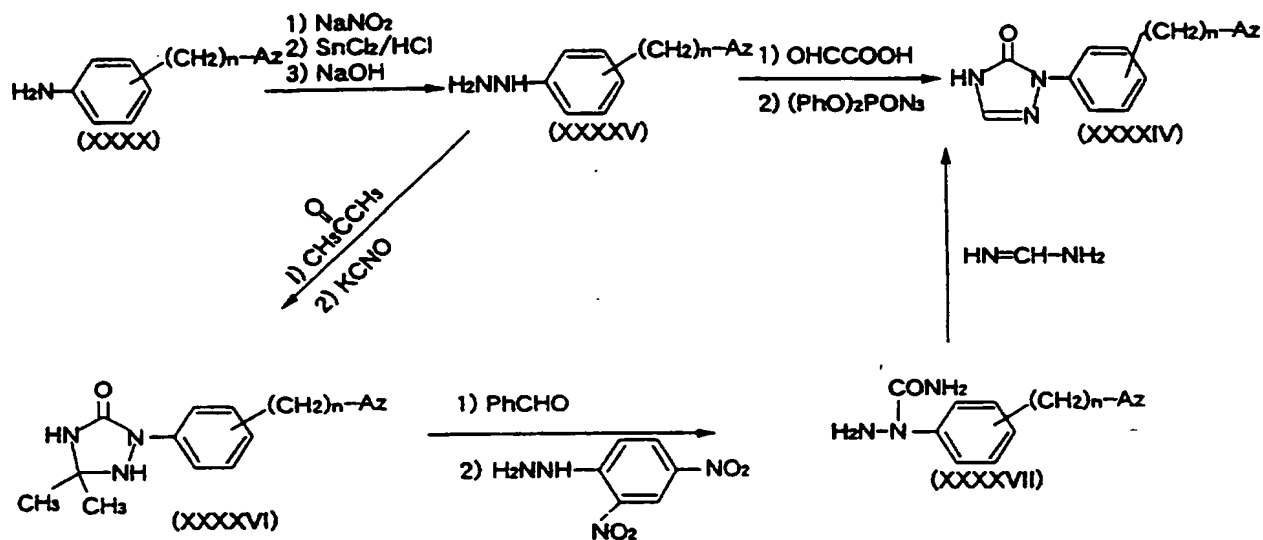


method represented by the following reaction scheme:



(wherein the symbols have the same meanings as defined above).

Further, the starting compound (V) or a salt thereof wherein A is  $-\text{CH}=\text{N}-$  [i.e., a compound (XXXXIV) or a salt thereof] can be prepared, for example, by a method represented by the reaction scheme:



(wherein the symbols have the same meanings as defined above).

The starting compounds or synthesized intermediate compounds above-obtained can be isolated and purified from the reaction mixtures by a known procedure per se such as extraction, concentration, neutralization, filtration, recrystallization, column chromatography, thin layer chromatography and the like. Alternatively the reactant mixture itself can be used as a material in the next step without isolation.

The compound of the present invention has low toxicity and exhibits potent antifungal activity with broad antifungal spectrum against, for example, microorganisms of genus

Candida (e.g., *Candida albicans*, *Candida utilis*, *Candida grabrata*, etc.), those of genus *Histoplasma* (e.g., *Histoplasma capsulatum*, etc.), those of genus *Aspergillus* (e.g., *Aspergillus niger*, *Aspergillus fumigatus*, etc.), those of genus *Cryptococcus* (e.g., *Cryptococcus neoformans*, etc.), those of genus *Trichophyton* (e.g., *Trichophyton rubrum*, *Trichophyton mentagrophytes*, etc.), those of genus *Microsporum* (e.g., *Microsporum gypseum*, etc.), those of genus *Malassezia* (e.g., *Malassezia furfur*, etc.) and the like. Accordingly, it can be used for prevention and treatment of the systemic fungal infection and dermatomycosis (e.g., candidiasis, histoplasmosis, aspergillosis, cryptococcosis, trichophytosis and microsporumosis) of mammals (e.g., human being, domestic animals and fowls) and further atopic dermatitis. Further, the compound of the invention can be used as an antifungal agent for agricultural use.

When the compound of the present invention is administered to a human being, it can be safely administered either orally or parenterally in the form of pharmaceutical compositions such as oral administration preparations (e.g., powders, granules, tablets, capsules), parenteral preparations [e.g., injections and external preparations (e.g., nasal and dermatological ones), suppositories (e.g., rectal and vaginal ones)] and the like in per se or in mixture with suitable pharmacologically-acceptable carriers, fillers or

diluents. The content of the compound of the present invention in a whole pharmaceutical composition is usually 5 to 100 wt%, preferably 20 to 100 wt% in an oral drug and 5 to 30 wt% in a parenteral drug.

Those preparations can be manufactured by methods which are known per se and commonly used in the manufacture of pharmaceutical preparations.

For example, the compound of the present invention can be made into an injection such as aqueous injections together with dispersing agents [e.g., Tween 80 (Atlas Powder, U.S.A.), HCO60 (Nikko Chemicals, Japan), carboxymethylcellulose or sodium alginate], preservatives (e.g., methylparaben, propylparaben, benzyl alcohol and chlorobutanol), isotonic agents (e.g., sodium chloride, glycerol, sorbitol and glucose) and the like, or as oily injections by dissolving, suspending or emulsifying in a plant oil (e.g., olive oil, sesame oil, peanut oil, cotton seed oil and corn oil), propylene glycol and the like.

In the manufacture of preparations for oral administration, the compound of the present invention is compression-molded together, for example, with fillers (e.g., lactose, sugar and starch), disintegrating agents (e.g., starch and calcium carbonate), binders (e.g., starch, arabic gum, carboxymethylcellulose, polyvinylpyrrolidone and hydroxypropylcellulose), lubricants (e.g., talc, magnesium stearate and polyethylene glycol 6000) and the like, followed, if

necessary, by coating in accordance with a known method per se with an object of taste-masking or of providing the preparation with enteric or sustained release property. Examples of the coating agents are hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (Rohm, West Germany; a copolymer of methacrylic acid with acrylic acid) and pigments such as titanium oxide and red iron oxide.

The compound of the present invention can be also used solid, semisolid or liquid preparations for external use. For example, in the case of solid external preparation, the compound of the present invention is made into the form of powdered compositions as it is or in a mixture with filler (e.g., glucose, mannitol, starch and microcrystalline cellulose), thickeners (e.g., natural gum, cellulose derivatives and acrylic acid polymers) and the like. In the case of semisolid external preparation, aqueous or oily gel preparation or ointment is preferred. In the case of liquid external preparation, the procedures are nearly the same as those in the case of injections to give oily or aqueous suspensions. pH Adjusting agents (e.g., carbonic acid, phosphoric acid, citric acid, hydrochloric acid and sodium hydroxide),

antiseptics (e.g., p-hydroxybenzoates, chlorobutanol and benzalkonium chloride) or the like can be added to the above-mentioned solid, semisolid or liquid preparations. More specifically, it can be used for sterilization of disinfection of skin or mucous membrane as an ointment containing, for example, about 0.1 to 100mg of the compound of the present invention per gram using Vaseline (petroleum jelly) or lanolin as a base material.

The compound of the present invention can be made into oily or aqueous solid, semisolid or liquid suppositories. Examples of the oily base materials used therefor are higher fatty acid glycerides [e.g., cacao butter and Witepsols (Dynamite-Nobel)], medium fatty acids (e.g., Migriols (Dynamite-Nobel)] or plant oil (e.g., sesame oil, soybean oil and cotton seed oil) and the like. Examples of the aqueous base materials are polyethylene glycols, propylene glycols, and those of the aqueous gel base materials are natural gums, cellulose derivatives, vinyl polymers, acrylic acid polymers.

The dose of the compound of the present invention may vary depending upon the state of infection, the route of administration or the like. In the case of orally administering it to an adult patient (weight: 50 kg) for the therapy of candidiasis, for example, it is about 0.01 to 100mg/kg/day and, preferably about 0.1 to 50mg/kg/day, and more preferably about 1 to 20mg/kg/day.

When the compound of the present invention is used as an agricultural antifungal agent, it may be dissolved or dispersed in a suitable liquid carrier (e.g., solvents), or mixed or absorbed with a suitable solid carrier (e.g., diluents and fillers), followed, if necessary, by addition of an emulsifier, suspending agent, spreader, penetrating agent, moisturizing agent, thickener, stabilizer, etc. to give the preparation a form such as emulsion, hydrating agent, powder, granules and the like. Such preparations can be prepared by known methods per se. The amount of the compound of the present invention is, for example, about 25 to 150g, preferably about 40 to 80g per acre of irrigated rice field for prevention of rice blast diseases.

Examples of the above liquid carrier are water, alcohols (e.g., methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol and ethylene glycol), ethers (e.g., dioxane, tetrahydrofran), aliphatic hydrocarbons (e.g., kerosene, lamp oil and fuel oil), aromatic hydrocarbons (e.g., benzene and toluene), halogenated hydrocarbons (e.g., methylene chloride and chloroform), acid amides (e.g., dimethylformamide and dimethylacetamido), esters (e.g., ethyl acetate and butyl acetate), nitrils (e.g., acetonitrile and propionitrile) and the like. They may be used either singly or as a mixture thereof in a suitable mixture ratio.

Examples of the above solid carriers are plant powder

(e.g., soybean powder, tobacco powder and wheat flour), mineral powder (e.g., kaolin and bentonite), alumina, sulfur powder, activated charcoal and the like. They may be used either individually or as a mixture thereof in a suitable mixing ratio.

#### BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is further described by way of the following Reference Examples and Working Examples.

$^1\text{H}$ -NMR spectra were measured by a spectrometer of Varian Gemini 200 type (200MHz) using tetramethylsilane as an internal standard. All  $\delta$  values are given by ppm. In the mixing solvents, the figures given in ( ) are the mixing ratio of each of the solvents by volume. Unless otherwise specified, the symbol % means by weight. In the silica gel chromatography, the ratio of the solvents is a ratio of the mixed solvents by volume.

The symbols used in the examples have the following meanings.

s: singlet; d: doublet; t: triplet; q: quartet; dd: double doublet; tt: triple triplet; m: multiplet; br: broad; J: coupling constant.

#### Reference Example 1

2-(2,4-Difluorophenyl)-2-[(1R)-1-(3,4,5,6-tetrahydro-2H-pyran-2-yl)oxyethyl]oxirane (82 g) (synthesized by the method disclosed in Japanese Unexamined Patent Publication



No. Hei 4(1992)-74168) and pyridinium p-toluenesulfonate (6.3 g) were dissolved in ethanol (600 ml), and the resultant was stirred at 55°C for 1 hour and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (1 lit.) and washed with water (200 ml x 2). The aqueous layer was extracted with ethyl acetate (100 ml x 2). The combined organic layers were washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate = 10/1 to 8/1 to 3/1) to give (1R)-1-[2-(2,4-difluorophenyl)-2-oxiranyl]ethanol (31.5 g) as a pale yellow oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.14-1.23 (3H,m), 1.77, 2.22 (1H), 2.80, 2.92 (1H), 3.27-3.32 (1H), 4.00-4.20 (1H,m), 6.75-6.94 (2H,m), 7.36-7.48 (1H,m)

#### Reference Example 2

(1R)-1-[2-(2,4-Difluorophenyl)-2-oxiranyl]ethanol (31.5 g) and 3,5-dinitrobenzoyl chloride (40 g) were dissolved in methylene chloride (500 ml), to which trimethylamine (24.1 ml) was added dropwise at ice-bath temperature. After the mixture was stirred at room temperature for 3.5 hours, it was washed with water (150 ml) and 5% sodium bicarbonate aqueous solution successively, dried over magnesium sulfate and concentrated under reduced pressure. The precipitated crystals were filtrated and washed with methylene chloride.

The mother liquor and the washings were combined and distilled off under reduced pressure. Ethyl acetate (25 ml) and methanol (300 ml) were added to the residue, and the mixture was cooled in an ice bath. The precipitated crystals were collected by filtration and recrystallized from a mixture of ethyl acetate (25 ml) and methanol (250 ml) to give [(1R)-1-[(2R)-2-(2,4-difluorophenyl)-2-oxiranyl]ethyl] 3,5-dinitrobenzoate (28.7 g) as colorless needles.

mp: 104-107°C (recrystallized from ethylacetate-hexane)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.46 (3H,dd,J=6.6Hz,J=1.2Hz), 3.01 (1H,d,J=4.6Hz), 3.23 (1H,d,J=4.6Hz), 5.33 (1H,q,J=6.6Hz), 6.85-7.07 (2H,m), 7.54 (1H,m), 9.13 (2H,d,J=2.2Hz), 9.25 (1H,t,J=2.2Hz)

### Reference Example 3

[(1R)-1-[(2R)-2-(2,4-Difluorophenyl)-2-oxiranyl]ethyl] 3,5-dinitrobenzoate (50 g) was dissolved in methanol (2 lit.), to which 1N-sodium hydroxide (255 ml) was added dropwise at room temperature. The mixture was stirred at room temperature for 1 hour and neutralized by an addition of 1 N-hydrochloric acid (127 ml) thereto. The resultant was concentrated under reduced pressure, to which ethyl acetate (1 lit.) and water (200 ml) were added. The mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride (200 ml), dried over magnesium sulfate and dis-

tilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: ethyl acetate/hexane = 1/3) to give (1R)-1-[(2R)-2-(2,4-difluorophenyl)-2-oxiranyl]ethanol (25 g) as a pale yellow oily substance.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.17 (3H,dd,J=6.6Hz,1.2Hz), 1.83 (1H,d,J=8Hz), 2.80 (1H,d,J=5.2Hz), 3.30 (1H,d,J=5.2Hz), 4.01-4.17 (1H,m), 6.75-6.93 (2H,m) 7.36-7.48 (1H,m)

#### Reference Example 4

To an ice-cooled solution of (1R)-1-[(2R)-2-(2,4-difluorophenyl)-2-oxiranyl]ethanol (16.1 g) in tetrahydrofuran (320 ml) were added triphenylphosphine (63.3 g), benzoic acid (29.5 g) and diethyl azodicarboxylate (42.0 g). The mixture was stirred at room temperature for 6 hours under an argon atmosphere. After ethyl acetate (800 ml) and water (500 ml) were added thereto, the separated aqueous layer was extracted with ethyl acetate (200 ml). The combined organic layers were washed with water and a saturated aqueous solution of sodium chloride successively, dried over magnesium sulfate and concentrated. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate = 15/1 to 7/1) to give [(1S)-1-[(2R)-2-(2,4-difluorophenyl)-2-oxiranyl]ethyl] benzoate (19.2 g) as a colorless oily substance.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.37 (3H,d,J=6.6Hz), 2.90 (1H,d,J=5.2Hz), 3.28 (1H,d,J=5.2Hz), 5.36 (1H,q,J=6.6Hz), 6.74-6.94 (2H,m),

7.38-7.60 (4H,m), 7.94-8.01 (2H,m)

IR  $\nu_{\max}^{\text{neat}}$   $\text{cm}^{-1}$ : 1725, 1615, 1600, 1505, 1450, 1425

[(1S)-1-[(2R)-2-(2,4-Difluorophenyl)-2-oxiranyl]-ethyl] benzoate (15.9 g) was dissolved in methanol (800 ml), to which 28% sodium methylate-methanol solution (12.9 ml) was added at ice-bath temperature and stirred at room temperature for 6 hours. After 1N-hydrochloric acid (63.2 ml) was added thereto, the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate = 6/1 to 2/1) to give (1S)-1-[(2R)-2-(2,4-difluorophenyl)-2-oxiranyl]ethanol (9.7 g) as a colorless oily substance.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.20 (3H,dd,J=6.4Hz,1Hz), 2.24 (1H,d,J=2Hz), 2.92 (1H,d,J=5Hz), 3.28 (1H,d,J=5Hz), 4.12 (1H,dq,J=6.4Hz,2Hz), 6.77-6.95 (2H,m), 7.32-7.44 (1H,m)  
IR  $\nu_{\max}^{\text{neat}}$   $\text{cm}^{-1}$ : 3420, 2980, 1615, 1600, 1500, 1425

#### Reference Example 5

2-(2-Fluorophenyl)-2-[(1R)-1-(3,4,5,6-tetrahydro-2H-pyran-2-yl)oxyethyl]oxirane (synthesized by the method disclosed in EP0548553A) was converted into [(1R)-1-[(2R)-2-(2-fluorophenyl)-2-oxiranyl]ethyl] 3,5-dinitrobenzoate by the method described in Reference Examples 1 and 2.  
Colorless prisms (recrystallized from ethyl acetate)  
mp: 183-184°C

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.47 (3H,dd,J=6.6Hz,1.6Hz), 3.03

(1H,d,J=4.7Hz), 3.23 (1H,d,J=4.7Hz), 5.35 (1H,q,J=6.6Hz),  
7.09-7.59 (4H,m), 9.13 (2H,d,J=2.2Hz), 9.23 (1H,t,J=2.2Hz)  
[ $\alpha$ ]<sub>D</sub><sup>23</sup> -24.7°C (c=1.0, in CHCl<sub>3</sub>)

Elemental analysis for C<sub>17</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>7</sub>

Calcd (%): C, 54.26; H, 3.48; N, 7.44

Found (%): C, 54.23; H, 3.25; N, 7.41

#### Reference Example 6

[(1R)-1-[(2R)-2-(2-Fluorophenyl)-2-oxiranyl]ethyl]  
3,5-dinitrobenzoate was converted into (1R)-1-[(2R)-2-(2-  
fluorophenyl)-2-oxiranyl]ethanol by the method described in  
Reference Example 3.

Colorless oily substance

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) $\delta$ : 1.17 (3H,dd,J=6.6Hz,1.0Hz), 1.78  
(1H,d,J=8.2Hz), 2.81 (1H,d,J=5.3Hz), 3.32 (1H,d,J=5.3Hz),  
4.09-4.23 (1H,m), 6.99-7.47 (4H,m)

#### Reference Example 7

(1R)-1-[(2R)-2-(2-Fluorophenyl)-2-oxiranyl]ethanol was  
converted into (1S)-1-[(2R)-2-(2-fluorophenyl)-2-oxiranyl]-  
ethanol by the method described in Reference Example 4.

Colorless oily substance

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) $\delta$ : 1.21 (3H,d,J=7Hz), 2.27 (1H,d,J=2Hz), 2.96  
(1H,d,J=5Hz), 3.30 (1H,d,J=5Hz), 4.16 (1H,dq,J=7Hz,2Hz),  
7.03-7.44 (4H,m)

#### Reference Example 8

2-(2-Fluorophenyl)-2-[(1R)-1-(3,4,5,6-tetrahydro-2H-  
pyran-2-yl)oxyethyl] oxirane (synthesized by the method de-

scribed in EP0548553A) was converted into (1R)-1-[2-(2-fluorophenyl)-2-oxiranyl]ethanol by the method described in Reference Example 1. To an ice-cooled solution of this compound (34.77 g) in tetrahydrofuran (600 ml) were added triphenylphosphine (127.21 g), 3,5-dinitrobenzoic acid (102.88 g) and diethyl azodicarboxylate (84.47 g). The mixture was stirred at room temperature for 7 hours under an argon atmosphere, and then ethyl acetate (600 ml), diisopropyl ether (100 ml) and water (800 ml) were added. The separated aqueous layer was extracted with ethyl acetate (600 ml, 400 ml). The organic layers were combined, washed with water and a saturated aqueous solution of sodium chloride successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate = 5/1) and recrystallized from ethyl acetate to give [(1S)-1-[(2R)-2-(2-fluorophenyl)-2-oxiranyl]ethyl] 3,5-dinitrobenzoate (23.15 g) as colorless needles.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.47 (3H,d,J=7Hz), 2.97 (1H,d,J=5Hz), 3.29 (1H,d,J=5Hz), 5.43 (1H,q,J=7Hz), 7.02-7.56 (4H,m), 9.06 (2H,d,J=2Hz), 9.21 (1H,t,J=2Hz)

This compound (22.91 g) was dissolved in methanol (700 ml), to which an aqueous solution of 1N-sodium hydroxide (146.5 ml) was added at ice-bath temperature. The mixture was stirred at room temperature for 1 hour. After 1N-hydro-

chloric acid (85.5 ml) was added thereto, the solvent was distilled off under reduced pressure. To the residue were added ethyl acetate (500 ml) and water (500 ml). The separated organic layer was washed with water and a saturated aqueous solution of sodium chloride successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate = 3/1) to give (1S)-1-[(2R)-2-(2-fluorophenyl)-2-oxiranyl]ethanol (10.76 g) as a colorless oily substance. The product was identical with the compound obtained in Reference Example 7.

#### Reference Example 9

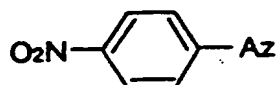
A mixture of 4-fluoronitrobenzene (3.1 g), 4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2H,4H)-1,2,4-triazolone (5.8 g), potassium carbonate (13.8 g) and N,N-dimethylformamide (60 ml) was stirred at 80°C for 2 hours. The resultant was cooled and poured into water (500 ml). The mixture was neutralized with hydrochloric acid and the precipitated crystals were collected by filtration. The crystals thus obtained were dissolved in ethyl acetate (300 ml) and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was crystallized from a mixture of ethyl acetate and diisopropyl ether to give 2-(4-nitrophenyl)-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2H,4H)-1,2,4-triazolone (5.5 g, 67%) as yellow crystalline powders.

mp: 161-162°C

Reference Examples 10 to 14

The compounds shown in Table 1 as below were obtained in the same manner as in Reference Example 9.

Table 1



Reference Example No.	Az	yield (%)	mp. (°C)
10	<chem>*N1C(=O)C=C(N1c2ccc(OCC(F)(F)F)cc2)C1=CC=CC=C1</chem>	75	117-118
11	<chem>*N1C(=O)C=C(N1c2ccc(OC(F)(F)F)cc2)C1=CC=CC=C1</chem>	70	143-145
12	<chem>*N1C(=O)C=C(N1c2ccc(CCC(F)(F)F)cc2)C1=CC=CC=C1</chem>	45	143-145
13	<chem>*N1C(=O)C=C(N1c2ccc(CCC(F)(F)F)cc2)C1=CC=CC=C1</chem>	83	198-199
14	<chem>*N1C(=O)C=C(N1c2ccc(CCC(F)(F)F)cc2)C1=CC=CC=C1</chem>	41	141-143

Reference Example 15

4-Fluoronitrobenzene (21 g) was reacted with 1H-1,2,3-triazole (12.4 g) in the same manner as in Reference Example 9. The resultant was cooled and poured into water. The precipitated crystals were collected by filtration and



purified by silica gel chromatography (eluent: dichloromethane to dichloromethane/acetone = 8/1). The first eluted fraction was recrystallized from dichloromethane-diisopropyl ether to give 2-(4-nitrophenyl)-2H-1,2,3-triazole (18.8 g) as pale yellow prisms.

mp: 183-184°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 7.90 (2H,s), 8.28 (2H,dt,J=9.4Hz,J=2.4Hz), 8.38 (2H,dt,J=9.4Hz,J=2.4Hz)

Further, the second eluted fraction was recrystallized from dichloromethane-diisopropyl ether to give 1-(4-nitrophenyl)-1H-1,2,3-triazole (6.02 g) as pale yellow prisms.

mp: 205-206°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 7.92 (1H,d,J=1.4Hz), 8.00 (2H,dt,J=9Hz,J=2.4Hz), 8.13 (1H,d,J=1.4Hz), 8.44 (2H,dt,J=9Hz,J=2.4Hz)

#### Reference Example 16

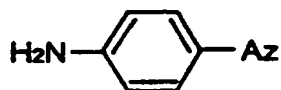
2-(4-Nitrophenyl)-4-[4-(2,2,3,3-tetrafluoropropoxy)-phenyl]-3(2H,4H)-1,2,4-triazolone (5.5 g) and 10% palladium-carbon (50% wet, 0.5 g) were added to methanol (200 ml). The mixture was subjected to catalytic hydrogenation at ordinary temperature under ordinary pressure. When hydrogen absorption stopped, dichloromethane (200 ml) was added thereto and the catalyst was removed by filtration. The catalyst was washed with dichloroethane (50 ml). The washings and the filtrate were combined and distilled

under reduced pressure to give 2-(4-aminophenyl)-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2H,4H)-1,2,4-triazolone (4.6 g, 90%) as a white solid. This compound was used for the next process without purification.

#### Reference Examples 17 to 21

The compounds shown in Table 2 as below were obtained in the same manner as in Reference Example 16.

Table 2



Reference Example No.	Az	yield (%)
17		97
18		94
19		96
20		100
21		95

#### Reference Example 22

Ferric chloride (0.2 g) and activated carbon (2.0 g)

were added to a solution of 1-(4-nitrophenyl)-3-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2(1H,3H)-imidazolone (20.5 g) in methanol-tetrahydrofran (75 ml:75 ml), to which hydrazine hydrate (8.0 ml) was added dropwise over the period of 10 minutes. After the mixture was refluxed with stirring for 14 hours, ferric chloride (0.2 g), activated carbon (2.0 g) and hydrazine hydrate (8.0 ml) were added thereto and the reaction mixture was refluxed with stirring for further 6 hours. The activated carbon was filtered off and washed with methanol (100 ml). The filtrate and the washing were combined and distilled off under reduced pressure. The residue thus obtained was dissolved in ethyl acetate (700 ml). The ethyl acetate layer was washed with water (200 ml X 4), dried over anhydrous magnesium sulfate and distilled off under reduced pressure to give 1-(4-aminophenyl)-3-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2(1H,3H)-imidazolone (18.1 g, 95%) as a pale yellow powder.

mp: 178-179°C

Elemental analysis for  $C_{18}H_{15}F_4N_3O_2$

Calcd (%): C, 56.70; H, 3.96; N, 11.02

Found (%): C, 56.58; H, 3.93; N, 11.21

#### Reference Example 23

In the same manner as in Reference Example 22, starting from 1-(4-nitrophenyl)-3-[4-(1,1,2,2-tetrafluoroethoxy)phenyl]-2(1H,3H)-imidazolone, 1-(4-aminophenyl)-3-[4-

(1,1,2,2-tetrafluoroethoxy)phenyl]-2(1H,3H)-imidazolone was obtained.

mp: 150-151°C

Elemental analysis for  $C_{17}H_{13}F_4N_3O_2$

Calcd (%): C, 55.59; H, 3.57; N, 11.44

Found (%): C, 55.74; H, 3.40; N, 11.49

#### Reference Example 24

2-(4-Aminophenyl)-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2H,4H)-1,2,4-triazolone (4.6 g) and pyridine (1.43 g) were dissolved in ethyl acetate (200 ml). To the resultant was added dropwise at room temperature a solution of phenyl chlorocarbonate (2.83 g) in ethyl acetate (20 ml). After the addition was completed, the reaction solution was stirred at room temperature for 2 hours. Water (200 ml), ethyl acetate (600 ml) and tetrahydrofuran (300 ml) were added thereto. The separated organic layer was washed with 5% phosphoric acid (200 ml X 2) and water (200 ml) successively, dried over anhydrous magnesium sulfate and filtrated. The filtrate was concentrated to about 50 ml and the precipitated crystals were collected by filtration. The crystals thus obtained were washed with diethyl ether and dried to give phenyl 4-[5-oxo-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-1H,4H-1,2,4-triazol-1-yl]phenylcarbamate (5.6 g, 93%) as colorless scaly crystals.

mp: 204-206°C

Elemental analysis for  $C_{24}H_{18}F_4N_4O_4$

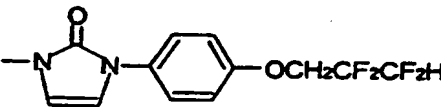
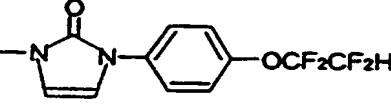
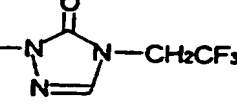
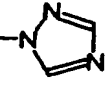
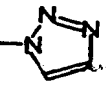
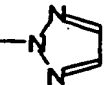
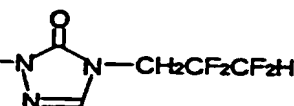
Calcd (%): C, 57.37; H, 3.61; N, 11.15

Found (%): C, 57.50; H, 3.67; N, 11.13

Reference Examples 25 to 31

The compounds shown in Table 3 as below were obtained in the same manner as in Reference Example 24.

Table 3

Reference Example No.	Az	yield (%)	mp. (°C)
25		89	243-244
26		95	208-211
27		87	183-184
28		90	157-160
29		96	195-200
30		89	143-144
31		84	173-175

Reference Example 32

Phenyl 4-[5-oxo-4-[4-(2,2,3,3-tetrafluoropropoxy)-phenyl]-1H,4H-1,2,4-triazol-1-yl]phenylcarbamate (5.6 g) was added to a mixture of ethanol (100 ml) and tetrahydrofuran (100 ml). To the resulting mixture was added hydrazine hydrate (3 g) with stirring. The resultant was stirred at 80°C for 2 hours and concentrated under reduce pressure to about 20 ml. After water (100 ml) was added, the precipitated crystals were collected by filtration, washed with ethanol and dried under reduced pressure to give 4-[4-[5-oxo-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-1H,4H-1,2,4-triazol-1-yl]phenyl]semicarbazide (4.8 g, 98%) as colorless prisms.

mp: >350°C

Elemental analysis for  $C_{18}H_{16}F_4N_6O_3$

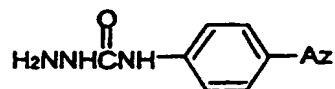
Calcd (%): C, 49.10; H, 3.66; N, 19.08

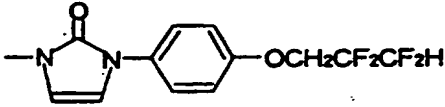
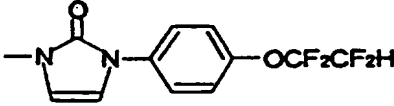
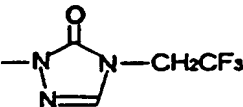
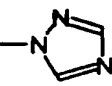
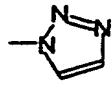
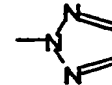
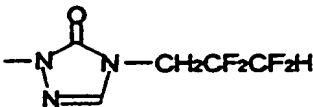
Found (%): C, 48.95; H, 3.72; N, 19.20

Reference Examples 33 to 39

The compounds shown in Table 4 as below were obtained in the same manner as in Reference Example 32.

Table 4



Reference Example No.	Az	yield (%)	mp. (°C)
33		95	>280
34		92	>250
35		90	275-280
36		95	228-232
37		98	225-234
38		96	275-277
39		95	265-274

Reference Example 40

4-[4-[5-Oxo-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-1H,4H-1,2,4-triazol-1-yl]phenyl]semicarbazide (4.75 g) was added to N,N-dimethylformamide (60 ml). To the mixture were

added acetic acid (4 g) and formamidine acetate (6 g), and the resulting mixture was stirred at room temperature for 3 hours and then at 80°C for 1.5 hours. After cooling, the reaction solution was diluted with water (30 ml). The precipitated crystals were collected by filtration and washed with water (100 ml). The crystals were dried and dissolved in a mixture of tetrahydrofuran (300 ml) and ethyl acetate (600 ml) with warming. The solution thus obtained was dried over anhydrous magnesium sulfate, filtrated and concentrated under reduced pressure. Ethyl acetate (50 ml) was added to the residue and the precipitated crystals were collected by filtration and recrystallized from tetrahydrofuran to give 4-[4-[5-oxo-4-[4-(2,2,3,3-tetrafluoropropoxy)-phenyl]-1H,4H-1,2,4-triazol-1-yl]phenyl]-3(2H,4H)-1,2,4-triazolone (2.4 g, 49%) as a white crystalline powder.  
mp: 297-298°C

Elemental analysis for  $C_{19}H_{14}F_4N_6O_3$

Calcd (%): C, 50.67; H, 3.13; N, 18.66

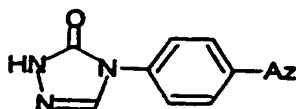
Found (%): C, 50.49; H, 3.20; N, 18.50

Reference Examples 41 to 47

The compounds shown in Table 5 as below were obtained in the same manner as in Reference Example 40.



Table 5



Reference Example No.	Az	yield (%)	mp. (°C)
41		52	>260
42		49	>260
43		71	>300
44		40	>300
45		58	>300
46		54	281-283
47		52	246-248

Reference Example 48

A mixture of phenyl 4-(1H-1,2,4-triazol-1-yl)phenylcarbamate (13 g), 2,2-diethoxyethyl amine (7.4 g) and pyridine (3.67 g) was heated at 50°C for 3 hours. The resultant was

cooled and the precipitated crystals were washed with a mixture of diisopropyl ether and petroleum ether (1:1, 100 ml x 2) to give 1-(2,2-diethoxyethyl)-3-[4-(1H-1,2,4-triazol-1-yl)phenyl]urea (14.5 g) as a colorless crystalline powder.

mp: 139-140°C

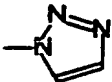
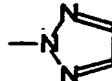
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.25 (6H,t,J=7.2Hz), 3.43 (2H,t,J=5Hz), 3.52-3.85 (4H,m), 4.57 (1H,t,J=5Hz), 5.08-5.18 (1H,m), 7.16 (1H,br), 7.49 (2H,d,J=9.4Hz), 7.57 (2H,d,J=9.4Hz), 8.08 (1H,s), 8.48 (1H,s)

#### Reference Examples 49 to 50

The compounds shown in Table 6 as below were obtained in the same manner as in Reference Example 48.

Table 6



Reference Example No.	Az	yield (%)	mp. (°C)
49		95	194-196
50		84	175-176

Reference Example 51

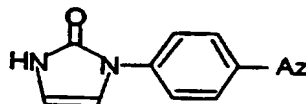
1-(2,2-Diethoxyethyl)-3-[4-(1H-1,2,4-triazol-1-yl)phenyl]urea (14.5 g) was dissolved in a mixture of methanol (214 ml) and water (85 ml), to which diluted hydrochloric acid (0.48 M, 104 ml) was added dropwise. After the reaction solution was stirred at room temperature for 14 hours, the precipitated crystals were collected by filtration to give 1-[4-(1H-1,2,4-triazol-1-yl)phenyl]-2-(1H,3H)-imidazolone (8.0 g) as a colorless crystalline powder. The filtrate was concentrated under reduced pressure to about 200 ml and the precipitated crystals were collected by filtration to give an additional amount (1.08 g) of the product.

mp: 294-296°C

Reference Examples 52 to 53

The compound shown in Table 7 as below were obtained in the same manner as in Reference Example 51.

Table 7



Reference Example No.	Az	yield (%)	mp. (°C)
52		86	255-257 (decomposition)
53		85	>300

Reference Example 54

To a solution of (1S)-1-[(2R)-2-(2,4-difluorophenyl)-2-oxiranyl]ethanol (1.0 g) in dichloromethane (14 ml) was added diisopropylethylamine (0.96 ml) at  $-78^{\circ}\text{C}$  in a nitrogen atmosphere, to which trifluoromethanesulfonic anhydride (0.93 ml) was added dropwise over the period of 5 minutes. After the reaction solution was stirred at  $-78^{\circ}\text{C}$  for 20 minutes and then at  $-25^{\circ}\text{C}$  for 25 minutes, the reaction solution was concentrated at  $-10^{\circ}\text{C}$  to about 10 ml. The concentrated solution was subjected to flash column chromatography using silica gel and eluted with dichloromethane-hexane (1:1). The desired fraction was concentrated to about 10 ml, and the residue was added at  $-14^{\circ}\text{C}$  to a solution prepared from 4-[4-[5-oxo-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-1H,4H-1,2,4-triazol-1-yl]phenyl]-3(2H,4H)-1,2,4-triazolone (2.1 g), dimethylformamide (40 ml), dimethyl sulfoxide (50 ml) and sodium hydride (60% in oil: 180 mg). The resulting mixture was stirred at  $-14^{\circ}\text{C}$  for 20 minutes and then at  $-5^{\circ}\text{C}$  for 20 minutes. The reaction solution was diluted with water (500 ml) and extracted with dichloromethane (300 ml X 2). The dichloromethane layer was washed with water (200 ml X 2) and a saturated aqueous solution of sodium chloride successively, dried over anhydrous magnesium sulfate and distilled off under reduced pressure to give a colorless powder. The product was purified by silica gel chromatography (eluent: hexane/ethyl

acetate = 1/1 to 1/2) and crystallized from ethyl acetate-hexane to give 2-[(1R,2S)-2-(2,4-difluorophenyl)-2,3-epoxy-1-methylpropyl]-4-[4-[5-oxo-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-1H-1,2,4-triazol-1-yl]phenyl]-3(2H,4H)-1,2,4-triazolone (0.29 g) as colorless crystalline powders.

mp: 181-183°C

Elemental analysis for  $C_{29}H_{22}F_6N_6O_4$

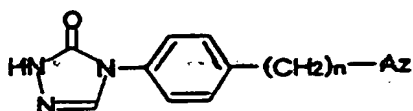
Calcd (%): C, 55.07; H, 3.51; N, 13.29

Found (%): C, 55.12; H, 3.34; N, 13.24

Reference Examples 55 to 63

The compounds shown in Table 8 as below were obtained in the same manner as in Reference Example 40.

Table 8

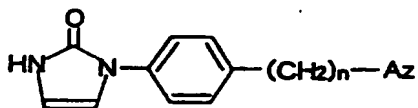


Reference Example No.	n	Az	mp. (°C)
55	1		249-250
56	0		269-270
57	1		201-205
58	0		284-286
59	0		245-248
60	1		250-252
61	0		282-284
62	0		280-283
63	0		243-248

Reference Examples 64 to 72

The compounds shown in Table 9 as below were obtained in the same manner as in Reference Example 51.

Table 9



Reference Example No.	n	Az	mp. (°C)
64	0		239-240
65	1		170-171
66	1		190-191
67	0		210-211
68	0		235-240
69	1		213-215
70	0		206-208
71	0		216-218
72	0		251-255

Reference Example 73

1-[4-(1H-1-Tetrazolyl)phenyl]-2(1H,3H)-imidazolone (5.0 g) was dissolved in acetic acid (500 ml) and 10% palladium-carbon (50% wet, 5.0 g) was added. The resulting mixture was stirred at 40°C for 4 hours under a hydrogen atmosphere. The catalyst was filtered and washed with acetic acid. The filtrate and the washings were combined and distilled off under reduced pressure. The residue was crystallized from ethanol to give 1-[4-(1H-1-tetrazolyl)phenyl]-2-imidazolidi-  
none (4.1 g) as colorless crystals.

mp: 237-240°C (dec.)

<sup>1</sup>H-NMR (d<sub>6</sub>-DMSO)δ: 3.45 (2H,t,J=7Hz), 3.93 (2H,t,J=7Hz),  
7.20 (1H,s), 7.82 (4H,s), 10.02 (1H,s)

Elemental analysis for C<sub>10</sub>H<sub>10</sub>N<sub>6</sub>O

Calcd (%): C,52.17; H,4.38; N,36.50

Found (%): C,51.99; H,4.33; N,36.41

Reference Example 74

Diisopropylethylamine (1.15 ml) was added to a solution of (1S)-1-[(2R)-2-(2,4-difluorophenyl)-2-oxiranyl]ethanol (1.20 g) in dichloromethane (26 ml) at -78°C under a nitrogen atmosphere, to which trifluoromethanesulfonic anhydride (1.10 ml) was added dropwise over the period of 5 minutes. The mixture was stirred at -78°C for 20 minutes and then at -30°C for 15 minutes. After addition of hexane (26 ml), the mixture was subjected to flash column chromatography using silica gel and eluted with dichloromethane-hexane (1:1).



The desired fraction was concentrated to about 20 ml, and the residue was added to a solution prepared from 1-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (940 mg), dimethylformamide (20 ml), dimethyl sulfoxide (10 ml), tetrahydrofuran (10 ml) and sodium hydride (72% in oil: 126 mg) at -30°C. The resulting mixture was stirred for 20 minutes at -30°C and then for 40 minutes at ice-bath temperature. Water (100 ml) was added and the mixture was extracted with ethyl acetate (150 ml). The ethyl acetate layer was washed with water (100 ml X 2) and a saturated aqueous solution of sodium chloride successively, dried over anhydrous magnesium sulfate and distilled off under reduced pressure to give a colorless powder. The product was purified by silica gel chromatography (eluent: hexane/ethyl acetate = 1/3) to give 1-[(1R,2S)-2-(2,4-difluorophenyl)-2,3-epoxy-1-methylpropyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (0.13 g) and (2R)-2-(2,4-difluorophenyl)-2-[(1R)-1-[1-[4-(1H-1-tetrazolyl)phenyl]-2-imidazolyl]oxy]ethyl]oxirane (0.05 g).

1-[(1R,2S)-2-(2,4-Difluorophenyl)-2,3-epoxy-1-methylpropyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone: colorless crystalline powder.

mp: 205-207°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.39(3H,d,J=7Hz), 2.73 (1H,d,J=5Hz), 2.83 (1H,d,J=5Hz), 5.09 (1H,q,J=7Hz), 6.52 (1H,d,J=3Hz), 6.66

(1H,d,J=3Hz), 6.81-6.96 (2H,m), 7.36-7.48 (1H,m), 7.78  
(2H,d,J=9Hz), 7.94 (2H,d,J=9Hz), 9.02 (1H,s)

SIMS (MH<sup>+</sup>): 411

Reference Example 75

Diisopropylethylamine (1.27 ml) was added to a solution of (1S)-1-[(2R)-2-(2-fluorophenyl)-2-oxiranyl]ethanol (1.21 g) in dichloromethane (25 ml) at -78°C under a nitrogen atmosphere, to which trifluoromethanesulfonic anhydride (1.22 ml) was added dropwise over a period of 5 minutes. The reaction solution was stirred at -78°C for 15 minutes and then at -30°C for 15 minutes. The resultant was diluted with hexane (25 ml), subjected to flash column chromatography using silica gel and eluted with dichloromethane-hexane (1:1). The desired fraction was concentrated to about 20 ml, and the residue was added to a solution prepared from 1-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (1.14 g), 1-methyl-2-pyrrolidone (30 ml) and 72% sodium hydride in oil (150 mg) at -30°C. The reaction solution was stirred at -30°C for 15 minutes and then at -10°C for 15 minutes. Water (100 ml) was added and the mixture was extracted with ethyl acetate (150 ml). The ethyl acetate layer was washed with water (100 ml) and a saturated aqueous solution of sodium chloride successively, dried over anhydrous magnesium sulfate and distilled off under reduced pressure to give a colorless powder. The product was purified by silica gel chromatography (eluent: hexane/ethyl acetate = 1/3) to give

1-[(1R,2S)-2-(2-fluorophenyl)-2,3-epoxy-1-methylpropyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (0.39 g) and (2R)-2-(2-fluorophenyl)-2-[(1R)-1-[1-[4-(1H-1-tetrazolyl)phenyl]-2-imidazolyl]oxy]ethyl]oxirane (0.18 g).

1-[(1R,2S)-2-(2-Fluorophenyl)-2,3-epoxy-1-methylpropyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone: colorless crystalline powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.39(3H,d,J=7Hz), 2.76 (1H,d,J=5Hz), 2.84 (1H,d,J=5Hz), 5.15 (1H,q,J=7Hz), 6.55 (1H,d,J=3Hz), 6.67 (1H,d,J=3Hz), 7.06-7.49 (4H,m), 7.79 (2H,d,J=9Hz), 7.96 (2H,d,J=9Hz), 9.04 (1H,s)

#### Reference Example 76

A mixture of (S)-ethyl lactate (75 g) and morpholine (164 g) was heated at 80°C for 64 hours. The reaction solution was concentrated and the residue was subjected to silica gel chromatography (eluent: hexane/ethyl acetate = 4/1 to ethyl acetate) to give 4-[(S)-2-hydroxypropionyl]-morpholine (69.4 g) as a pale yellow oily substance. p-Toluenesulfonic acid monohydrate (0.82 g) was added to a solution of 4-[(S)-2-hydroxypropionyl]morpholine (69.4 g) in dichloromethane (300 ml), to which 3,4-dihydro-2H-pyran (40.3 g) was added dropwise at ice-bath temperature. The reaction solution was stirred at 0°C for 30 minutes and washed with a 5% aqueous solution of sodium bicarbonate. After the organic layer was dried over anhydrous magnesium

sulfate and concentrated, the residue was subjected to silica gel chromatography (eluent: hexane/ethyl acetate = 8/1 to ethyl acetate) to give 4-[(2S)-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)propionyl]morpholine (89.1 g) as a pale yellow oily substance.

1-Bromo-2-fluorobenzene (15 g) and 4-[(2S)-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)propionyl]morpholine (40 g) were dissolved in tetrahydrofuran (200 ml), to which magnesium (turnings: 4.4 g) was added. The mixture was stirred vigorously. The reaction flask was cooled when the temperature of the reaction solution reached to 35°C, and 1-bromo-2-fluorobenzene (16.7 g) was added thereto over the period of 10 minutes while the temperature of the reaction solution was kept at 35 to 37°C. After the reaction solution was stirred at 30 to 35°C for 2 hours, it was cooled in an ice-bath. A saturated aqueous solution of ammonium chloride (100 ml) was added thereto and the mixture was extracted with ethyl acetate (200 ml x 2, 100 ml). The extract was washed with water and a saturated aqueous solution of sodium chloride successively, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was subjected to silica gel chromatography (eluent: hexane/ethyl acetate = 10/1 to 5/1) to give (2S)-2'-fluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-propiophenone (22.4 g) as a pale yellow oily substance.

(2S)-2'-Fluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-

xyloxy)propiophenone (25 g) was dissolved in ethanol (200 ml), to which pyridinium p-toluenesulfonate (1.28 g) was added. The reaction solution was stirred at 55°C for 2.5 hours and then concentrated. The residue was subjected to silica gel chromatography (eluent: hexane/ethyl acetate = 9/1 to 5/1) to give (2S)-2'-fluoro-2-hydroxypropiophenone (16.4 g) as a colorless oily substance.

IR(neat): 1690 (C=O)  $\text{cm}^{-1}$

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.41(3H,dd,J=7Hz,J=1.4Hz), 3.78 (1H,d,J=6Hz), 4.98-5.15 (1H,m), 7.12-7.36 (2H,m), 7.54-7.68 (1H,m), 7.90-8.00 (1H,m)

#### Reference Example 77

(2S)-2',4'-Difluoro-2-hydroxypropiophenone (synthesized by the method disclosed in Japanese Unexamined Patent Publication No. Hei 5(1993)-230038: 26.01 g) was dissolved in dichloromethane (300 ml), to which diisopropylethylamine (19.90 g) was added at -60°C under a nitrogen atmosphere, and then trifluoromethanesulfonic anhydride (25.90 ml) was added thereto dropwise over the period of 20 minutes. After the reaction temperature was gradually raised to -30°C, the reaction solution was further stirred for 30 minutes. The reaction solution was purified by silica gel chromatography (silica gel 400 g, eluent: dichloromethane/hexane = 1/1) to give (2S)-2',4'-difluoro-2-trifluoromethanesulfonyloxypropiophenone (39.21 g) as a pale yellow oily substance.

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) $\delta$ : 1.73(3H,dd,J=7.0Hz,1.6Hz), 5.93  
(1H,q,J=7.0Hz), 6.90-7.12 (2H,m), 8.03  
(1H,dt,J=6.4Hz,8.6Hz)  
 $[\alpha]_D^{23} + 29.2^\circ$  (c=1.12, in MeOH)

#### Reference Example 78

(2S)-2'-Fluoro-2-hydroxypropiophenone (synthesized by the method disclosed in Reference Example 76: 3.36 g) was dissolved in dichloromethane (30 ml). To the resultant was added diisopropylethylamine (4.18 ml) at  $-60^\circ\text{C}$  under a nitrogen atmosphere, and then trifluoromethanesulfonic anhydride (4.03 ml) was added dropwise to the mixture over the period of 2 minutes. After the reaction temperature was gradually raised to  $-25^\circ\text{C}$ , the reaction solution was stirred for 30 minutes. The reaction solution was purified by silica gel chromatography (silica gel 60 g, eluent: dichloromethane/hexane = 1/1) to give (2S)-2'-fluoro-2-trifluoromethanesulfonyloxypropiophenone (5.30 g) as a pale yellow oily substance.

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) $\delta$ : 1.73(3H,dd,J=7Hz,J=1.6Hz), 6.49  
(1H,q,J=7Hz), 7.15-7.38 (2H,m), 7.58-7.72 (1H,m), 7.97  
(1H,dt,J=1.8Hz,J=7.6Hz)

#### Reference Example 79

1-[4-(1H-1,2,4-Triazol-1-yl)phenyl]-2(1H,3H)-imidazolone (3.39 g) was dissolved in 1-methyl-2-pyrrolidone (220 ml), to which 72% sodium hydride in oil (528 mg) was added. The mixture was stirred at room temperature for 1

hour. The reaction solution was cooled in an ice-bath and added dropwise over the period of 15 minutes to a solution of (2S)-2'-fluoro-2-trifluoromethanesulfonyloxypropiophenone (4.7 g) in tetrahydrofuran (100 ml) which had been cooled to -20°C. After the addition was complete, the reaction temperature was raised to 10°C over 30 minutes and the reaction solution was further stirred for 12 hours. The reaction solution was diluted with acetic acid (10 ml) and ethyl acetate (500 ml), washed with water (250 ml x 2), 0.5 hydrochloric acid (250 ml x 2) and a saturated aqueous solution of sodium chloride (250 ml) successively, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (silica gel, eluent: hexane/ethyl acetate/acetic acid = 1/4/0.06) and recrystallized from diisopropyl ether (25 ml) to give 1-[(1R)-2-fluorophenyl]-2-oxo-1-methylethyl]-3-[4-(1H-1,2,4-triazol-1-yl)phenyl]-2(1H,3H)-imidazolone as a colorless crystalline powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.65(3H,d,J=7.2Hz), 5.82 (1H,q,J=7.2Hz), 6.64 (1H,d,J=3.2Hz), 6.70 (1H,d,J=3.2Hz), 7.14-7.31 (2H,m), 7.53-7.94 (6H,m), 8.11 (1H,s), 8.56 (1H,s)

#### Reference Example 80

1-[4-(1H-1-Tetrazolyl)phenyl]-2(1H,3H)-imidazolone (0.94 g) was dissolved in 1-methyl-2-pyrrolidone (25 ml), to which 72% sodium hydride in oil (0.126 g) was added. The

reaction solution was stirred at room temperature for 30 minutes. The resultant was ice-cooled and added dropwise over the period of 10 minutes to a solution of (2S)-2'-fluoro-2-trifluoromethanesulfonyloxypropiophenone (1.57 g) in tetrahydrofuran (25 ml) which had been cooled to  $-10^{\circ}\text{C}$ . After the addition was complete, the reaction temperature was raised to  $0^{\circ}\text{C}$  over 15 minutes and the reaction solution was stirred for 30 minutes. The reaction solution was diluted with acetic acid (3 ml) and ethyl acetate (100 ml), washed with water (50 ml x 2), 0.5 N-hydrochloric acid (50 ml x 2) and a saturated aqueous solution of sodium chloride (50 ml) successively, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate/acetic acid = 1/3/0.05) and recrystallized from diisopropyl ether (20 ml) to give 1-[(1R)-2-fluorophenyl]-2-oxo-1-methylethyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (0.22 g) as a colorless crystalline powder.

mp:  $162-164^{\circ}\text{C}$

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.66 (3H, d,  $J=7.2\text{Hz}$ ), 5.83 (1H, q,  $J=7.2\text{Hz}$ ), 6.67 (1H, d,  $J=3.2\text{Hz}$ ), 6.74 (1H, d,  $J=3.2\text{Hz}$ ), 7.16-7.33 (2H, m), 7.54-7.98 (2H, m), 7.77 (2H, d,  $J=9\text{Hz}$ ), 7.91 (2H, d,  $J=9\text{Hz}$ ), 9.03 (1H, s)

#### Reference Example 81

Chloromethylisopropoxydimethylsilane (2.14 g) and



magnesium (for Grignard reaction, 313 mg) were added to tetrahydrofuran (15 ml), and the mixture was heated to 60°C. To the mixture was added magnesium in the form of turnings which had been activated by methyl iodide, and then the mixture was stirred in a bath at 60°C for 3 hours.

The solution of the Grignard reagent thus obtained was added dropwise to a solution of 1-[(1R)-2-(2-fluorophenyl)-2-oxo-1-methylethyl]-3-[4-(1H-1-tetrazolyl)phenyl-2(1H,3H)-imidazolone (1 g) in tetrahydrofuran (150 ml) over the period of 10 minutes at ice-bath temperature, and the mixture was stirred for 30 minutes. A cooled saturated aqueous solution of ammonium chloride (30 ml) and cooled water (100 ml) were added thereto at ice-bath temperature and the mixture was extracted with ethyl acetate (200 ml). The extract was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from a mixture of diisopropyl ether and ethyl acetate to give 1-[(1R,2S)-2-(2-fluorophenyl)-2-hydroxy-3-(isopropoxydimethylsilyl)-1-methylpropyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (637 mg) as a colorless crystalline powder.

<sup>1</sup>H-NMR (d<sub>6</sub>-DMSO)δ: -0.30(3H,s), -0.28 (3H,s), 0.99-1.64 (11H,m), 3.83 (1H,quintet,J=6Hz), 4.81 (1H,q,J=7Hz), 5.21 (1H,br), 6.93-7.77 (6H,m), 8.05 (2H,d,J=9Hz), 8.17

(2H,d,J=9Hz), 10.17 (1H,s)

Reference Example 82

1-[(1R,2S)-2-(2-Fluorophenyl)-2-hydroxy-3-(isopropoxy dimethylsilyl)-1-methylpropyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (1 g) was dissolved in a mixture of methanol and tetrahydrofuran (1:1, 20 ml), to which an 30% aqueous solution of hydrogen peroxide (2 ml) and sodium bicarbonate (157 mg) were added. The mixture was heated at 50°C for 4 hours, then cooled and extracted with ethyl acetate (100 ml). The extract was washed with water (30 ml), an aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (30 ml x 2) and a saturated aqueous solution of sodium chloride (30 ml) successively, dried over magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate = 1/4) and recrystallized from diethyl ether (20 ml) to give 1-[(1R,2S)-2-(2-fluorophenyl)-2,3-dihydroxy-1-methyl propyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (440 mg) as a colorless crystalline powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.17(3H,d,J=7Hz), 3.52-3.62 (1H,m), 4.05-4.18 (2H,m), 5.01 (1H,q,J=7Hz), 6.72 (1H,d,J=3.2Hz), 6.82 (1H,d,J=3.2Hz), 7.01-7.33 (3H,m), 7.70-7.78 (1H,m), 7.90 (2H,d,J=9Hz), 7.99 (2H,d,J=9Hz), 9.55 (1H,s)

Reference Example 83

1-[(1R,2S)-2-(2-Fluorophenyl)-2,3-dihydroxy-1-methyl propyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone

(440 mg) was dissolved in a mixture of ethyl acetate and tetrahydrofuran (1:2, 30 ml), to which methanesulfonyl chloride (0.18 g) and triethylamine (0.16 g) were added dropwise at ice-bath temperature. The reaction solution was stirred at 0°C for 30 minutes and washed with water (15 ml x 2) and a saturated aqueous solution of sodium chloride (15 ml) successively. The organic layer was dried over magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate = 1/4) to give 1-[(1R,2S)-2-(2-fluorophenyl)-2-hydroxy-3-methanesulfonyloxy-1-methylpropyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (330 mg) as a colorless crystalline powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.27(3H,d,J=7Hz), 2.87 (3H,s), 4.54 (1H,d,J=12Hz), 4.73-4.88 (2H,m), 6.63 (1H,d,J=3.2Hz), 6.72 (1H,d,J=3.2Hz), 7.09-7.39 (3H,m), 7.75-7.94 (1H,m), 7.81 (2H,d,J=9Hz), 7.93 (2H,d,J=9Hz), 9.04 (1H,s)

#### Reference Example 84

1-[(1R,2S)-2-(2-Fluorophenyl)-2-hydroxy-3-methanesulfonyloxy-1-methylpropyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (100 mg) was dissolved in dimethylformamide (4 ml), to which potassium carbonate (42 mg) was added, and the mixture was heated at 40°C for 1 hour. The resultant was diluted with ethyl acetate (20 ml) and washed with water (10 ml) and a saturated aqueous solution of

sodium chloride (10 ml) successively. The organic layer was dried over magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate = 1/4). The desired fraction was concentrated and the residue was recrystallized from diisopropyl ether to give 1-[(1R,2S)-2-(2-fluorophenyl)-2,3-epoxy-1-methylpropyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (58 mg) as a colorless crystalline powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.40 (3H,d,J=7Hz), 2.76 (1H,d,J=5Hz), 2.84 (1H,d,J=5Hz), 5.15 (1H,q,J=7Hz), 6.55 (1H,d,J=3.2Hz), 6.67 (1H,d,J=3.2Hz), 7.07-7.48 (4H,m), 7.79 (2H,d,J=9Hz), 7.95 (2H,d,J=9Hz), 9.05 (1H,s)

#### Working Example 1

60% sodium hydride in oil (108 mg) was dispersed in dimethylformamide (4 ml), to which 1,2,4-triazole (207 mg) was added at ice-bath temperature, and the mixture was stirred at room temperature for 10 minutes. To the resultant was added a solution of 2-[(1R, 2S)-2-(2,4-difluorophenyl)-2,3-epoxy-1-methylpropyl]-4-[4-[5-oxo-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-1H-1,2,4-triazol-1-yl]phenyl]-3(2H,4H)-1,2,4-triazolone (560 mg) in dimethylformamide (2 ml), and the mixture was heated at 60°C for 11 hours. After cooling, water (40 ml) and ethyl acetate (40 ml) were added to the mixture. The separated aqueous layer was extracted

with ethyl acetate twice. The combined ethyl acetate layers were washed with water and a saturated aqueous solution of sodium chloride successively, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: ethyl acetate/hexane = 19/1 to ethyl acetate) and then by reverse phase chromatography (eluent: ethanol/water = 4/1) to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-[5-oxo-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-1H-1,2,4-triazol-1-yl]phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 1; 0.21g) as a colorless powder.

$[\alpha]_D^{20} -16.9^\circ$  (c=1.0% in MeOH)

Elemental analysis for  $C_{31}H_{25}F_6N_9O_4 \cdot 0.5H_2O$

Calcd (%): C, 52.40; H, 3.69; N, 17.74

Found (%): C, 52.59; H, 3.67; N, 17.69

#### Working Example 2

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (1.2g), 4-[4-[2-oxo-3-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-1H,3H-imidazol-1-yl]phenyl]-3(2H,4H)-1,2,4-triazolone (2.2 g) and potassium carbonate (powder: 3.5 g) were added to N,N-dimethylformamide (50 ml), and the mixture was heated with stirring at 90°C for 42 hours. After cooling, the resultant was diluted with ethyl acetate (150 ml) and tetrahydrofuran (50 ml). Ice water (150 ml) was added thereto to separate the ethyl

acetate layer. The aqueous layer was extracted with ethyl acetate (100 ml). The ethyl acetate layers were combined and washed with 0.5N-sodium hydroxide (100 ml), 1N-hydrochloric acid (100 ml) and a saturated aqueous solution of sodium chloride (100 ml) successively. The ethyl acetate layer was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (elute:ethyl acetate/acetone = 10/1) and crystallized from tetrahydrofuran-diisopropyl ether to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-[2-oxo-3-[4-(2,2,3,3-tetrafluoropropoxy)-phenyl]-1H,3H-imidazol-1-yl]phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 2; 0.26g) as a colorless crystalline powder. mp: 181-183°C

Elemental analysis for  $C_{32}H_{26}F_6N_8O_4$

Calcd (%): C, 54.86; H, 3.74; N, 15.99

Found (%): C, 54.58; H, 3.75; N, 15.71

$[\alpha]_D^{20}$  -18.9° (c=1.0% in MeOH)

### Working Example 3

2-[(1R,2R)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-[2-oxo-3-[4-(1,1,2,2-tetrafluoroethoxy)phenyl]-1H,3H-imidazol-1-yl]phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 3) was obtained in the same manner as in Working Example 2,

Colorless crystalline powder

mp: 214-215°C

Elemental analysis for  $C_{31}H_{24}F_6N_8O_4$

Calcd (%): C, 54.23; H, 3.52; N, 16.32

Found (%): C, 54.05; H, 3.37; N, 16.32

$[\alpha]_D^{20}$  -19.0° (c=1.0% in MeOH)

#### Working Example 4

A mixture of 60% sodium hydride in oil (0.24 g) and dimethyl sulfoxide (60 ml) was stirred at 80°C for 30 minutes. To the mixture was added 4-[4-[5-oxo-4-(2,2,2-trifluoroethyl)-1H,4H-1,2,4-triazol-1-yl]phenyl]-3-(2H,4H)-1,2,4-triazolone (1.94 g), and the mixture was stirred for 5 minutes. To the resultant was added (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (1.0 g), and the mixture was stirred at 80°C for 24 hours under an argon atmosphere. The reaction solution was cooled, diluted with ethyl acetate (300 ml) and washed with water (50 ml X 2) and a saturated aqueous solution of sodium chloride (50 ml) successively. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate = 1/2 to ethyl acetate) to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-[5-oxo-4-[4-(2,2,2-trifluoroethyl)-1H,4H-1,2,4-triazol-1-yl]phenyl]-3-(2H,4H)-1,2,4-triazolone (Compound 4; 0.46 g) as a pale yellow powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.31(3H,d,J=7Hz), 4.36 (2H,q,J=8.4Hz), 4.37 (1H,d,J=14Hz), 5.03 (1H,d,J=14Hz), 5.10 (1H,q,J=7Hz), 5.44 (1H,s), 6.75-6.88 (2H,m), 7.48-7.65 (1H,m), 7.67 (2H,d,J=9Hz), 7.68 (1H,s), 7.69 (1H,s), 7.83 (1H,s), 7.94 (1H,s), 8.16 (2H,d,J=9Hz)

#### Working Example 5

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (1.0 g) was reacted with 4-[4-(1H-1,2,4-triazol-1-yl)phenyl]-3(2H,4H)-1,2,4-triazolone (0.91 g) in the same manner as in Working Example 4 to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(1H-1,2,4-triazol-1-yl)phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 5; 0.54 g). Colorless crystalline powder

mp: 182-184°C

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.32(3H,d,J=7Hz), 4.40 (1H,d,J=14.4Hz), 5.03 (1H,d,J=14.4Hz), 5.11 (1H,q,J=7Hz), 5.41 (1H,s), 6.75-6.90 (2H,m), 7.50-7.65 (1H,m), 7.69 (1H,s), 7.79 (2H,d,J=9Hz), 7.88 (2H,d,J=9Hz), 7.92 (1H,s), 7.96 (1H,s), 8.14(1H,s), 8.65 (1H,s)

Elemental analysis for  $\text{C}_{22}\text{H}_{19}\text{F}_2\text{N}_9\text{O}_2$

Calcd (%): C,55.11; H,3.99; N,26.29

Found (%): C,55.05; H,4.01; N,26.14

IR(KBr): 1714, 1618, 1556, 1527, 1394 $\text{cm}^{-1}$



Working Example 6

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (1.0 g) was reacted with 4-[4-(1H-1,2,3-triazol-1-yl)phenyl]-3(2H,4H)-1,2,4-triazolone (1.09 g) in the same manner as in Working Example 4 to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(1H-1,2,3-triazol-1-yl)phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 6; 0.27 g).

Colorless crystalline powder

mp: 219-220°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.32(3H,d,J=7Hz), 4.40 (1H,d,J=14.2Hz), 5.03 (1H,d,J=14.2Hz), 5.10 (1H,q,J=7Hz), 5.38 (1H,s), 6.75-6.90 (2H,m), 7.50-7.65 (1H,m), 7.70 (1H,s), 7.82 (2H,d,J=9Hz), 7.88 (1H,s), 7.90 (1H,s), 7.94 (2H,d,J=9Hz), 7.94 (1H,s), 8.05 (1H,s)

Elemental analysis for C<sub>22</sub>H<sub>19</sub>F<sub>2</sub>N<sub>9</sub>O<sub>2</sub>

Calcd (%): C,55.11; H,3.99; N,26.29

Found (%): C,54.91; H,3.97; N,26.26

IR(KBr): 1700, 1675, 1618, 1556, 1527, 1502cm<sup>-1</sup>

Working Example 7

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (1.0 g) was reacted with 4-[4-(2H-1,2,3-triazol-2-yl)phenyl]-3(2H,4H)-1,2,4-triazolone (1.09 g) in the same manner as in Working Example 4 to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(2H-1,2,3-triazol-2-

yl)phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 7; 0.65 g).

Pale yellow plates

mp: 213-215°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.32(3H,d,J=7Hz), 4.38 (1H,d,J=14.2Hz),  
5.04 (1H,d,J=14.2Hz), 5.11 (1H,q,J=7Hz), 5.42 (1H,s), 6.75-  
6.90 (2H,m), 7.50-7.64 (1H,m), 7.69 (1H,s), 7.74  
(2H,d,J=9Hz), 7.85 (2H,s), 7.86 (1H,s), 7.95 (1H,s),  
8.25(2H,d,J=9Hz)

Elemental analysis for C<sub>22</sub>H<sub>19</sub>F<sub>2</sub>N<sub>9</sub>O<sub>2</sub>

Calcd (%): C,55.11; H,3.99; N,26.29

Found (%): C,54.97; H,3.96; N,26.29

IR(KBr): 1697, 1623, 1602, 1564, 1519, 1510cm<sup>-1</sup>

#### Working Example 8

2-[(1R,2R)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-[5-oxo-4-[4-(2,2,3,3-tetrafluoropropyl)-1H,4H-1,2,4-triazol-1-yl]phenyl]-3-(2H,4H)-1,2,4-triazolone (Compound 8) was obtained in the same manner as in Working Example 4.

Pale yellow powder

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.31(3H,d,J=7Hz), 4.34 (2H,t,J=14Hz), 4.37  
(1H,d,J=14Hz), 5.04 (1H,d,J=14Hz), 5.10 (1H,q,J=7Hz), 5.46  
(1H,s), 5.98 (1H,tt,J=53Hz,J=2.4Hz), 6.75-6.90 (2H,m),  
7.50-7.65 (1H,m), 7.67 (2H,d,J=9Hz), 7.68 (1H,s), 7.72  
(1H,s), 7.86 (1H,s), 7.96 (1H,s), 8.16 (2H,d,J=9Hz)

Working Example 9

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (2.5 g), 1-[4-(1H-1,2,4-triazol-1-yl)phenyl]-2(1H,3H)-imidazolone (2.72 g) and cesium carbonate (powder: 9.7 g) were added to N,N-dimethylformamide (150 ml), and the mixture was heated at 80°C with stirring for 9.5 hours. After cooling, the reaction mixture was diluted with ethyl acetate (400 ml). Ice water (150 ml) was added thereto to separate the ethyl acetate layer. The aqueous layer was extracted with ethyl acetate (100 ml). The ethyl acetate layers were combined and washed with 0.5N-sodium hydroxide (100 ml), 1N-hydrochloric acid (100 ml x 2) and a saturated aqueous solution of sodium chloride (50 ml) successively. The ethyl acetate layer was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: ethyl acetate/acetone = 2/1) to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,4-triazol-1-yl)phenyl]-2(1H,3H)-imidazolone (Compound 9; 1.03 g) as a pale yellow powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.21 (3H,d,J=7Hz), 4.22 (1H,d,J=14.2Hz), 5.01 (1H,q,J=7Hz), 5.12 (1H,d,J=14.2Hz), 5.50 (1H,br), 6.72 (1H,d,J=3.2Hz), 6.73-6.90 (2H,m), 6.83 (1H,d,J=3.2Hz), 7.40-7.55 (1H,m), 7.75 (1H,s), 7.78 (2H,d,J=9.4Hz), 7.86 (1H,s), 7.86 (2H,d,J=9.4Hz), 8.13 (1H,s), 8.59 (1H,s)

IR(KBr): 3400, 3118, 1683, 1616, 1527, 1500cm<sup>-1</sup>

Working Example 10

1-[(1R,2R)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,4-triazol-1-yl)phenyl]-2-(1H,3H)-imidazolone (0.50 g) obtained in Working Example 9 was dissolved in acetic acid (25 ml), to which 10% palladium-carbon (200 mg) was added. The resultant was stirred under a hydrogen atmosphere at room temperature for 3 hours and then at 50°C for 3 hours. After the catalyst was filtered off, the filtrate was concentrated. The residue was purified by silica gel chromatography (eluent: ethyl acetate/acetone = 5/1 to 2/1) and recrystallized from ethyl acetate-diisopropyl ether to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,4-triazol-1-yl)phenyl]-2-imidazolidinone (Compound 10; 0.37 g) as a colorless crystalline powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.08(3H,d,J=7.2Hz), 3.68-4.18 (4H,m), 4.52 (1H,d,J=14Hz), 4.58-4.80 (1H,m), 5.12 (1H,d,J=14Hz), 5.38 (1H,br), 6.70-6.86 (2H,m), 7.35-7.50 (1H,m), 7.66 (2H,dt,J=9.4Hz,J=2.4Hz), 7.75 (2H,dt,J=9.4Hz,J=2.4Hz), 7.77 (1H,s), 7.87 (1H,s), 8.11 (1H,s), 8.53 (1H,s)

Elemental analysis for C<sub>23</sub>H<sub>22</sub>F<sub>2</sub>N<sub>8</sub>O<sub>2</sub>

Calcd (%): C,57.50; H,4.62; N,23.32

Found (%): C,57.46; H,4.47; N,23.19

IR(KBr): 3390, 3106, 1677, 1614, 1523, 1484cm<sup>-1</sup>

Working Example 11

To a mixture of 1-[4-(1H-1,2,3-triazol-1-yl)phenyl]-2(1H,3H)-imidazolone (2.72 g) and 1-methyl-2-pyrrolidone (100 ml) was added sodium hydride (70% in oil, 0.40 g), and the mixture was stirred at room temperature for 1 hour. (2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (2.51 g) was added thereto, and the mixture was stirred at 100°C for 8 hours under an argon atmosphere. After cooling, the reaction solution was diluted with ethyl acetate (400 ml), and washed with water (100 ml), 1N-hydrochloric acid (100 ml X 2) and a saturated aqueous solution of sodium chloride (50 ml) successively. The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: ethyl acetate to ethyl acetate/acetone = 5/1) and recrystallized from ethyl acetate-diisopropyl ether to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,3-triazol-1-yl)phenyl]-2(1H,3H)-imidazolone (Compound 11; 1.82 g) as a pale yellow crystalline powder.

mp: 178-181°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.22(3H,d,J=7Hz), 4.22 (1H,d,J=14.4Hz), 5.01 (1H,q,J=7Hz), 5.12 (1H,d,J=14.4Hz), 5.38 (1H,br), 6.70-6.88 (4H,m), 7.40-7.55 (1H,m), 7.76 (1H,s), 7.80-7.93

(6H,m), 8.03 (1H,s)

Elemental analysis for  $C_{23}H_{20}F_2N_8O_2$

Calcd (%): C, 57.74; H, 4.21; N, 23.42

Found (%): C, 57.46; H, 4.25; N, 23.30

IR(KBr): 1691, 1656, 1619, 1527, 1502, 1430 $cm^{-1}$

Working Example 12

1-[(1R,2R)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,3-triazol-1-yl)phenyl]-2(1H,3H)-imidazolone (0.80 g) obtained in Working Example 11 was subjected to catalytic hydrogenation in the same manner as in Working Example 10 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,3-triazol-1-yl)phenyl]-2-imidazolidinone (Compound 12; 0.69 g).

Colorless crystalline powder

$^1H$ -NMR ( $CDCl_3$ ) $\delta$ : 1.08(3H,d,J=7Hz), 3.70-4.14 (4H,m), 4.52 (1H,d,J=14.2Hz), 4.60-4.78 (1H,m), 5.12 (1H,d,J=14.2Hz), 5.38 (1H,br), 6.70-6.86 (2H,m), 7.35-7.50 (1H,m), 7.68-7.82 (4H,m), 7.77 (1H,s), 7.86 (2H,s), 7.97 (1H,s)

Elemental analysis for  $C_{23}H_{22}F_2N_8O_2$

Calcd (%): C, 57.50; H, 4.62; N, 23.32

Found (%): C, 57.38; H, 4.59; N, 23.41

IR(KBr): 1697, 1664, 1618, 1527, 1502, 1427 $cm^{-1}$

Working Example 13

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (2.51 g) was reacted with 1-[4-(2H-1,2,3-triazol-2-yl)phenyl]-2(1H,3H)-imidazolone (2.72 g) in the same manner as in Working Example 11 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(2H-1,2,3-triazol-2-yl)phenyl]-2(1H,3H)-imidazolone (Compound 13; 1.41 g).

Pale yellow needles

mp: 182-185°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.22(3H,d,J=7Hz), 4.22 (1H,d,J=14.4Hz), 4.99 (1H,q,J=7Hz), 5.01 (1H,d,J=14.4Hz), 5.13 (1H,br), 6.70-6.88 (4H,m), 7.40-7.56 (1H,m), 7.75 (1H,s), 7.81 (2H,d,J=9.2Hz), 7.84 (2H,s), 7.86 (1H,s), 8.18 (2H,d,J=9.2Hz)

Elemental analysis for C<sub>23</sub>H<sub>20</sub>F<sub>2</sub>N<sub>8</sub>O<sub>2</sub>

Calcd (%): C,57.74; H,4.21; N,23.42

Found (%): C,57.67; H,4.20; N,23.59

IR(KBr): 3328, 1664, 1614, 1519, 1430, 1384cm<sup>-1</sup>

Working Example 14

1-[(1R,2R)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(2H-1,2,3-triazol-2-yl)phenyl]-2(1H,3H)-imidazolone (0.80 g) obtained in Working Example 13 was subjected to catalytic hydrogenation in the same manner as in Working Example 10 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-

1-yl)propyl]-3-[4-(2H-1,2,3-triazol-2-yl)phenyl]-2-imidazol-  
idinone (Compound 14; 0.70 g).

Colorless crystalline powder

mp: 196-197°C

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.08 (3H, d,  $J=7.4\text{Hz}$ ), 3.68-4.12 (4H, m), 4.53  
(1H, d,  $J=14\text{Hz}$ ), 4.58-4.76 (1H, m), 5.13 (1H, d,  $J=14\text{Hz}$ ), 5.42  
(1H, br), 6.70-6.85 (2H, m), 7.36-7.50 (1H, m), 7.71  
(2H, d,  $J=9\text{Hz}$ ), 7.76 (1H, s), 7.81 (2H, s), 7.87 (1H, s), 8.07  
(2H, d,  $J=9\text{Hz}$ )

IR(KBr): 3426, 1687, 1658, 1616, 1517, 1484  $\text{cm}^{-1}$

#### Working Example 15

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-  
triazol-1-yl)methyloxirane was reacted with 1-[4-(1H-1-  
pyrazolyl)phenyl]-2(1H,3H)-imidazolone in the same manner as  
in Working Example 11 to give 1-[(1R,2R)-2-(2,4-difluoro-  
phenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-  
3-[4-(1H-1-pyrazolyl)phenyl]-2(1H,3H)-imidazolone (Compound  
15).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.21 (3H, d,  $J=7\text{Hz}$ ), 4.22 (1H, d,  $J=14.4\text{Hz}$ ),  
4.98 (1H, q,  $J=7\text{Hz}$ ), 5.12 (1H, d,  $J=14.4\text{Hz}$ ), 5.56 (1H, br),  
6.47-6.54 (1H, m), 6.68-6.88 (4H, m), 7.40-7.56 (1H, m), 7.70-  
7.85 (6H, m), 7.85 (1H, s), 7.94 (1H, d,  $J=2.4\text{Hz}$ )

Elemental analysis for  $\text{C}_{24}\text{H}_{21}\text{F}_2\text{N}_7\text{O}_2$

Calcd (%): C, 60.37; H, 4.43; N, 20.53

Found (%): C, 60.29; H, 4.42; N, 20.50



Working Example 16

1-[(1R,2R)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1-pyrazolyl)phenyl]-2(1H,3H)-imidazolone (Compound 15) obtained in Working Example 15 was subjected to catalytic hydrogenation in the same manner as in Working Example 10 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1-pyrazolyl)phenyl]-2-imidazolidinone (Compound 16).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.08 (3H,d,J=7Hz), 3.65-4.10 (4H,m), 4.53 (1H,d,J=14.2Hz), 4.55-4.75(1H,m), 5.12 (1H,d,J=14.2Hz), 5.45 (1H,br), 6.46-6.48 (1H,m), 6.70-6.85 (2H,m), 7.35-7.50 (1H,m), 7.60-7.75 (5H,m), 7.76 (1H,s), 7.88 (1H,s), 7.90 (1H,d,J=2.6Hz)

Elemental analysis for C<sub>24</sub>H<sub>23</sub>F<sub>2</sub>N<sub>7</sub>O<sub>2</sub>

Calcd (%): C,60.12; H,4.83; N,20.45

Found (%): C,60.02; H,4.95; N,20.34

Working Example 17

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 1-[4-(1H-1,2,4-triazol-1-ylmethyl)phenyl]-2(1H,3H)-imidazolone in the same manner as in Working Example 11 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,4-triazol-1-ylmethyl)phenyl]-2(1H,3H)-imidazolone (Compound 17).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.20 (3H,d,J=7Hz), 4.19 (1H,d,J=14.4Hz),

4.97 (1H,q,J=7Hz), 5.10 (1H,d,J=14.4Hz), 5.37 (2H,s), 5.55 (1H,br), 6.65 (1H,d,J=3.2Hz), 6.70-6.90 (3H,m), 7.37 (2H,d,J=8.6Hz), 7.35-7.55 (1H,m), 7.69 (2H,d,J=8.6Hz), 7.74 (1H,s), 7.85 (1H,s), 7.99 (1H,s), 8.10 (1H,s)

Working Example 18

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 4-[4-(1H-1,2,4-triazol-1-ylmethyl)phenyl]-3(2H,4H)-1,2,4-triazolone in the same manner as in Working Example 11 to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(1H-1,2,4-triazol-1-ylmethyl)phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 18).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.30 (3H,d,J=7.2Hz), 4.36 (1H,d,J=14.2Hz), 5.02 (1H,d,J=14.2Hz), 5.09 (1H,q,J=7.2Hz), 5.42 (2H,s), 5.43 (1H,s), 6.75-6.90 (2H,m), 7.43 (2H,d,J=8.6Hz), 7.50-7.67 (1H,m), 7.63 (2H,d,J=8.6Hz), 7.69 (1H,s), 7.82 (1H,s), 7.94 (1H,s), 8.01 (1H,s), 8.15 (1H,s)

Working Example 19

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 4-[4-(1H-1-pyrazolyl)phenyl]-3(2H,4H)-1,2,4-triazolone in the same manner as in Working Example 11 to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(1H-1-pyrazolyl)phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 19).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.32 (3H,d,J=7Hz), 4.38 (1H,d,J=14.4Hz), 5.05 (1H,d,J=14.4Hz), 5.11 (1H,q,J=7Hz), 5.45 (1H,s), 6.52-6.54 (1H,m), 6.76-6.90 (2H,m), 7.50-7.65 (1H,m), 7.65-7.93 (7H,m), 7.96 (1H,s), 7.98 (1H,d,J=2.6Hz)

Working Example 20

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 1-[4-(2H-1,2,3-triazol-2-ylmethyl)phenyl]-2(1H,3H)-imidazolone in the same manner as in Working Example 11 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(2H-1,2,3-triazol-2-ylmethyl)phenyl]-2(1H,3H)-imidazolone (Compound 20).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.19 (3H,d,J=7Hz), 4.17 (1H,d,J=14.4Hz), 4.95 (1H,q,J=7Hz), 5.09 (1H,d,J=14.4Hz), 5.55 (1H,br), 5.63 (2H,s), 6.63 (1H,d,J=3.2Hz), 6.70-6.86 (3H,m), 7.40-7.55 (1H,m), 7.42 (2H,d,J=8.6Hz), 7.64 (2H,s), 7.64 (2H,d,J=8.6Hz), 7.73 (1H,s), 7.85 (1H,s)

Working Example 21

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 4-[4-(2H-1,2,3-triazol-2-ylmethyl)phenyl]-3(2H,4H)-1,2,4-triazolone in the same manner as in Working Example 11 to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(2H-1,2,3-triazol-2-ylmethyl)phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 21).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.29 (3H,d,J=7Hz), 4.34 (1H,d,J=14.4Hz),

5.02 (1H,d,J=14.4Hz), 5.08 (1H,q,J=7Hz), 5.44 (1H,s), 5.66 (2H,s), 6.73-6.87 (2H,m), 7.46 (2H,d,J=8.6Hz), 7.50-7.62 (1H,m), 7.58 (2H,d,J=8.6Hz), 7.66 (2H,s), 7.68 (1H,s), 7.78 (1H,s), 7.94 (1H,s)

Elemental analysis for  $C_{23}H_{21}F_2N_9O_2$

Calcd (%): C,55.98; H,4.29; N,25.55

Found (%): C,55.87; H,4.18; N,25.42

#### Working Example 22

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 4-[4-(1H-1-imidazolyl)phenyl]-3(2H,4H)-1,2,4-triazolone in the same manner as in Working Example 11 to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(1H-1-imidazolyl)phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 22).

$^1H$ -NMR ( $CDCl_3$ ) $\delta$ : 1.32 (3H,d,J=7Hz), 4.40 (1H,d,J=14Hz), 5.03 (1H,d,J=14Hz), 5.11 (1H,q,J=7Hz), 5.42 (1H,s), 6.73-6.88 (2H,m), 7.26 (1H,s), 7.33 (1H,s), 7.51-7.65 (1H,m), 7.57 (2H,d,J=9Hz), 7.71 (1H,s), 7.76 (2H,d,J=9Hz), 7.86 (1H,s), 7.91 (1H,s), 7.95 (1H,s)

#### Working Example 23

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 1-[4-(1H-1-imidazolyl)phenyl]-2(1H,3H)-imidazolone in the same manner as in Working Example 11 to give 1-[(1R,2R)-2-(2,4-

difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1-imidazolyl)phenyl]-2(1H,3H)-imidazolone (Compound 23).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.21 (3H,d,J=7Hz), 4.22 (1H,d,J=14Hz), 5.00 (1H,q,J=7Hz), 5.12 (1H,d,J=14Hz), 5.56 (1H,br), 6.70 (1H,d,J=3Hz), 6.76-6.86 (3H,m), 7.23 (1H,s), 7.30 (1H,s), 7.42-7.54 (1H,m), 7.49 (2H,d,J=8Hz), 7.75 (1H,s), 7.78 (1H,s), 7.84 (2H,d,J=8Hz), 7.86 (1H,s)

#### Working Example 24

1-[(1R,2R)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-imidazolyl)phenyl]-2(1H,3H)-imidazolone (Compound 23) obtained in Working Example 23 was subjected to catalytic hydrogenation in the same manner as in Working Example 10 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1-imidazolyl)phenyl]-2-imidazolidinone (Compound 24).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.08 (3H,d,J=7Hz), 3.70-4.08 (4H,m), 4.52 (1H,d,J=14Hz), 4.55-4.76 (1H,m), 5.11 (1H,d,J=14Hz), 5.40 (1H,br), 6.73-6.84 (2H,m), 7.20 (1H,s), 7.26 (1H,s), 7.36-7.50 (1H,m), 7.39 (2H,d,J=9Hz), 7.69 (2H,d,J=9Hz), 7.76 (1H,s), 7.82 (1H,s), 7.87 (1H,s)

#### Working Example 25

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 4-[4-(2H-2-tetrazolyl)phenyl]-3(2H,4H)-1,2,4-triazolone in the same

manner as in Working Example 11 to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(2H-2-tetrazolyl)phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 25).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.33 (3H,d,J=7Hz), 4.40 (1H,d,J=14Hz), 5.04 (1H,d,J=14Hz), 5.11 (1H,q,J=7Hz), 5.37 (1H,s), 6.77-6.88 (2H,m), 7.52-7.64 (1H,m), 7.71 (1H,s), 7.87 (2H,d,J=9Hz), 7.92 (1H,s), 7.95 (1H,s), 8.34 (2H,d,J=9Hz), 8.71 (1H,s)

Elemental analysis for  $\text{C}_{21}\text{H}_{18}\text{F}_2\text{N}_{10}\text{O}_2$

Calcd (%): C, 52.50; H, 3.78; N, 29.15

Found (%): C, 52.36; H, 3.85; N, 29.02

#### Working Example 26

(2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 1-[4-(2H-2-tetrazolyl)phenyl]-2(1H,3H)-imidazolone in the same manner as in Working Example 11 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(2H-2-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (Compound 26).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.21 (3H,d,J=7Hz), 4.22 (1H,d,J=14Hz), 5.02 (1H,q,J=7Hz), 5.12 (1H,d,J=14Hz), 5.49 (1H,br), 6.75 (1H,d,J=3Hz), 6.75-6.85 (2H,m), 6.85 (1H,d,J=3Hz), 7.42-7.54 (1H,m), 7.76 (1H,s), 7.85 (1H,s), 7.93 (2H,d,J=9Hz), 8.25 (2H,d,J=9Hz), 8.68 (1H,s)

Working Example 27

1-[(1R,2R)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(2H-2-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (Compound 26) obtained in Working Example 26 was subjected to catalytic hydrogenation in the same manner as in Working Example 10 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-tri-azol-1-yl)propyl]-3-[4-(2H-2-tetrazolyl)phenyl]-2-imidazolidinone (Compound 27).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.08 (3H,d,J=7Hz), 3.69-3.81 (1H,m), 3.94-4.10 (3H,m), 4.52 (1H,d,J=14Hz), 4.62-4.80 (1H,m), 5.13 (1H,d,J=14Hz), 5.25-5.50 (1H,br), 6.72-6.84 (2H,m), 7.36-7.49 (1H,m), 7.77 (1H,s), 7.80 (2H,d,J=9Hz), 7.86 (1H,s), 8.13 (2H,d,J=9Hz), 8.64 (1H,s)

Working Example 28

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 1-[4-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-2(1H,3H)-imidazolone in the same manner as in Working Example 11 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-2(1H,3H)-imidazolone (Compound 28).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.20 (3H,d,J=7Hz), 4.19 (1H,d,J=14Hz), 4.97 (1H,q,J=7Hz), 5.09 (1H,d,J=14Hz), 5.55 (1H,br), 5.59 (2H,s), 6.65 (1H,d,J=3.2Hz), 6.75-6.90 (3H,m), 7.35-7.55 (4H,m), 7.66-7.75 (4H,m), 7.84 (1H,s)

Working Example 29

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 4-[4-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3(2H,4H)-1,2,4-triazolone in the same manner as in Working Example 2 to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(1H-1,2,3-triazol-1-ylmethyl)-phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 29).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.30 (3H,d,J=7Hz), 4.36 (1H,d,J=14Hz), 5.00 (1H,d,J=14Hz), 5.08 (1H,q,J=7Hz), 5.41 (1H,s), 5.63 (2H,s), 6.75-6.90 (2H,m), 7.40-7.64 (6H,m), 7.69 (1H,s), 7.76 (1H,s), 7.80 (1H,s), 7.94 (1H,s)

Working Example 30

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 1-[4-(2-methyl-4-thiazolyl)phenyl]-2(1H,3H)-imidazolone in the same manner as in Working Example 11 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(2-methyl-4-thiazolyl)phenyl]-2(1H,3H)-imidazolone (Compound 30).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.21 (3H,d,J=7Hz), 2.78 (3H,s), 4.22 (1H,d,J=14Hz), 4.98 (1H,q,J=7Hz), 5.12 (1H,d,J=14Hz), 5.60 (1H,br), 6.70-6.85 (4H,m), 7.33 (1H,s), 7.40-7.55 (1H,m), 7.69-8.00 (6H,m)



Working Example 31

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 4-[4-(2-methyl-4-thiazolyl)phenyl]-3(2H,4H)-1,2,4-triazolone in the same manner as in Working Example 2 to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(2-methyl-4-thiazolyl)phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 31).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.31 (3H,d,J=7Hz), 2.79 (3H,s), 4.37 (1H,d,J=14Hz), 5.04 (1H,d,J=14Hz), 5.11 (1H,q,J=7Hz), 5.47 (1H,s), 6.77-6.90 (2H,m), 7.39 (1H,s), 7.50-7.70 (4H,m), 7.85-8.05 (4H,m)

Working Example 32

(2R,3S)-2-(2-Fluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 1-[4-(1H-1,2,3-triazol-1-yl)phenyl]-2(1H,3H)-imidazolone in the same manner as in Working Example 11 to give 1-[(1R,2R)-2-(2-fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,3-triazol-1-yl)phenyl]-2(1H,3H)-imidazolone (Compound 32).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.21 (3H,d,J=7Hz), 4.23 (1H,d,J=14.2Hz), 5.08 (1H,q,J=7Hz), 5.17 (1H,d,J=14.2Hz), 5.36 (1H,br), 6.73 (1H,d,J=3.2Hz), 6.86 (1H,d,J=3.2Hz), 6.99-7.09 (2H,m), 7.19-7.52 (2H,m), 7.51-7.92 (6H,m), 7.80 (1H,s), 8.03 (1H,s)

Elemental analysis for C<sub>23</sub>H<sub>21</sub>FN<sub>8</sub>O<sub>2</sub>

Calcd (%): C, 59.99; H, 4.60; N, 24.23

Found (%): C, 59.62; H, 4.61; N, 24.13

Working Example 33

(2R,3S)-2-(2-Fluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 1-[4-(2H-1,2,3-triazol-2-yl)propyl]-2(1H,3H)-imidazolone to give 1-[(1R,2R)-2-(2-fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propoxy]-3-[4-(2H-1,2,3-triazol-2-yl)phenyl]-2(1H,3H)-imidazolone (Compound 33).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.21 (3H,d,J=7Hz), 4.23 (1H,d,J=14Hz), 5.07 (1H,q,J=7Hz), 5.18 (1H,d,J=14Hz), 5.37 (1H,br), 6.70 (1H,d,J=3.2Hz), 6.83 (1H,d,J=3.2Hz), 6.98-7.08 (2H,m), 7.19-7.51 (2H,m), 7.73 (1H,s), 7.75 (2H,d,J=9.2Hz), 7.83 (2H,s), 7.85 (1H,s), 8.17 (2H,d,J=9.2Hz)

Elemental analysis for C<sub>23</sub>H<sub>21</sub>FN<sub>8</sub>O<sub>2</sub>

Calcd (%): C, 59.99; H, 4.60; N, 24.33

Found (%): C, 59.80; H, 4.58; N, 23.87

Working Example 34

1-[(1R,2R)-2-(2-Fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,3-triazol-1-yl)phenyl]-2(1H,3H)-imidazolone (compound 32) obtained in Working Example 32 was subjected to catalytic hydrogenation in the same manner as in Working Example 10 to give 1-[(1R,2R)-2-(2-fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,3-triazol-1-yl)phenyl]-2-imidazolidinone (Compound 34).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.08 (3H,d,J=7Hz), 3.72-4.14 (4H,m), 4.54 (1H,d,J=14.2Hz), 4.70-4.84 (1H,m), 5.17 (1H,d,J=14.2Hz), 5.30 (1H,br), 6.96-7.08 (2H,m), 7.18-7.50 (2H,m), 7.68-7.78 (4H,m), 7.75 (1H,s), 7.84 (2H,s), 7.98 (1H,s)

Elemental analysis for  $\text{C}_{23}\text{H}_{23}\text{FN}_8\text{O}_2$

Calcd (%): C,59.73; H,5.01; N,24.23

Found (%): C,59.32; H,4.99; N,24.00

Working Example 35

1-[(1R,2R)-2-(2-Fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,3-triazol-1-yl)propyl]-3-[4-(2H-1,2,3-triazol-2-yl)phenyl]-2(1H,3H)-imidazolone (Compound 33) obtained in Working Example 33 was subjected to catalytic hydrogenation in the same manner as in Working Example 10 to give 1-[(1R,2R)-2-(2-fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(2H-1,2,3-triazol-2-yl)phenyl]-2-imidazolidinone (Compound 35).

mp.: 178-179°C

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.08 (3H,d,J=7Hz), 3.71-4.07 (4H,m), 4.54 (1H,d,J=14Hz), 4.74-4.77 (1H,m), 5.18 (1H,d,J=14Hz), 5.38 (1H,br), 6.96-7.06 (2H,m), 7.16-7.51 (2H,m), 7.71 (2H,d,J=9Hz), 7.74 (1H,s), 7.80 (2H,s), 7.83 (1H,s), 8.07 (2H,d,J=9Hz)

Elemental analysis for  $\text{C}_{23}\text{H}_{23}\text{FN}_8\text{O}_2$

Calcd (%): C,59.73; H,5.01; N,24.23

Found (%): C,59.49; H,5.23; N,24.01

Working Example 36

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (0.50 g), 4-[4-(2-methyl-4-oxazolyl)phenyl]-3(2H,4H)-1,2,4-triazolone (0.56 g) and potassium carbonate (powder: 1.38 g) were added to a mixture of 1-methyl-2-pyrrolidone (5 ml) and N,N-dimethylformamide (4 ml), and the mixture was heated with stirring at 90°C for 20 hours. After cooling, the reaction solution was diluted with ethyl acetate (40 ml). Ice water (40 ml) was added thereto to separate the ethyl acetate layer. The ethyl acetate layer was washed with 0.5N-sodium hydroxide (40 ml), 1N-hydrochloric acid (40 ml) and a saturated aqueous solution of sodium chloride (40 ml) successively. The ethyl acetate layer was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: ethyl acetate to ethyl acetate/methanol = 9/1) and crystallized from ethyl acetate-diisopropyl ether to give 2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(2-methyl-4-oxazolyl)phenyl]-3(2H,4H)-1,2,4-triazolone (Compound 36, 0.33 g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.31 (3H,d,J=7Hz), 2.54 (3H,s), 4.36 (1H,d,J=14Hz), 5.04 (1H,d,J=14Hz), 5.10 (1H,q,J=7Hz), 5.47 (1H,s), 6.77-6.88 (2H,m), 7.51-7.69 (4H,m), 7.85 (1H,s), 7.86 (2H,d,J=8Hz), 7.88 (1H,s), 7.96 (1H,s).

Working Example 37

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane was reacted with 1-[4-(2-methyl-4-oxazolyl)phenyl]-2(1H,3H)-imidazolone in the same manner as in Working Example 11 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(2-methyl-4-oxazolyl)phenyl]-2(1H,3H)-imidazolone (Compound 37).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.21 (3H,d,J=7Hz), 2.53 (3H,s), 4.21 (1H,d,J=14Hz), 4.97 (1H,q,J=7Hz), 5.12 (1H,d,J=14Hz), 5.60 (1H,br), 6.69-6.86 (4H,m), 7.42-7.55 (1H,m), 7.69 (2H,d,J=9Hz), 7.73 (1H,s), 7.80 (2H,d,J=9Hz), 7.84 (1H,s), 7.86 (1H,s)

Working Example 38

(2R,3S)-2-(2-fluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (2.24 g), 1-[4-(1H-1,2,4-triazol-1-yl)phenyl]-2(1H,3H)-imidazolone (2.17 g) and cesium carbonate (powder: 7.76 g) were added to dimethylsulfoxide (100 ml), and the mixture was heated with stirring at 100°C. for 17 hours. After being cooled, the reaction solution was diluted with ethyl acetate (200 ml). Ice water (200 ml) was added thereto to separate the ethyl acetate layer. The aqueous layer was extracted with ethyl acetate (100 ml). The ethyl acetate layers were combined and washed with 0.5N-sodium hydroxide (100 ml), 1N-hydrochloric acid (100 ml x 2) and a saturated aqueous solution of sodium chloride

(100 ml) successively. The ethyl acetate layer was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: ethyl acetate/acetone = 4/1) to give 1-[(1R,2R)-2-(2-fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-[1H-1,2,4-triazol-1-yl)phenyl]-2(1H,3H)-imidazolone (Compound 38; 0.45 g).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.21 (3H,d,J=7Hz), 4.23 (1H,d,J=14Hz), 5.02 (1H,q,J=7Hz), 5.17 (1H,d,J=14Hz), 5.37 (1H,br), 6.71 (1H,d,J=3.2Hz), 6.86 (1H,d,J=3.2Hz), 6.99-7.10 (2H,m), 7.20-7.52 (2H,m), 7.70-7.89 (6H,m), 8.13 (1H,s), 8.58 (1H,s)

#### Working Example 39

1-[(1R,2R)-2-(2-Fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,4-triazol-1-yl)phenyl]-2(1H,3H)-imidazolone (Compound 38) obtained in Working Example 38 was subjected to catalytic hydrogenation in the same manner as in Working Example 10 to give 1-[(1R,2R)-2-(2-fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,4-triazol-1-yl)phenyl]-2-imidazolidinone (Compound 39).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.08 (3H,d,J=7Hz), 3.72-4.10 (4H,m), 4.53 (1H,d,J=14.2Hz), 4.76-4.79 (1H,m), 5.17 (1H,d,J=14.2Hz), 5.19 (1H,br), 6.97-7.09 (2H,m), 7.17-7.46 (2H,m), 7.63-7.77 (5H,m), 7.82 (1H,s), 8.10 (1H,s), 8.52 (1H,s)

Elemental analysis for  $C_{23}H_{23}FN_8O_2$

Calcd (%): C, 59.73; H, 5.01; N, 24.23

Found (%): C, 59.33; H, 5.03; N, 23.98

Working Example 40

(2R,3S)-2-(2-Fluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (2.34 g), 1-[4-(2H-2-tetrazolyl)-phenyl]-2(1H,3H)-imidazolone (2.28 g) and cesium carbonate (powder: 6.52 g) were added to 1-methyl-2-pyrroli done (100 ml), and the mixture was heated at 80°C for 18 hours with stirring. The reaction solution was cooled, diluted with ethyl acetate (200 ml) and added to ice water (200 ml) to separate the ethyl acetate layer. The aqueous layer was extracted with ethyl acetate (100 ml). The combined ethyl acetate layers were washed with 1N-hydrochloric acid (100 ml x 2) and a saturated aqueous solution of sodium chloride (100 ml) successively. The ethyl acetate layer was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: hexane/acetone = 1/1) to give 1-[(1R,2R)-2-(2-fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(2H-2-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (Compound 40; 0.494 g) as a colorless crystalline powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.21 (3H,d,J=7Hz), 4.23 (1H,d,J=14Hz), 5.10 (1H,q,J=7Hz), 5.19 (1H,d,J=14Hz), 5.34 (1H,br), 6.75 (1H,d,J=3.2Hz), 6.88 (1H,d,J=3.2Hz), 6.99-7.09 (2H,m),

7.20-7.51 (2H,m), 7.75 (1H,s), 7.81 (1H,s), 7.94  
(2H,d,J=9Hz), 8.25 (2H,d,J=9Hz), 8.68 (1H,s)

Elemental analysis for  $C_{22}H_{20}FN_9O_2$

Calcd (%): C, 57.26; H, 4.37; N, 27.32

Found (%): C, 57.19; H, 4.29; N, 27.07

#### Working Example 41

1-[(1R,2R)-2-(2-Fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(2H-2-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (Compound 40) obtained in Working Example 40 was subjected to catalytic hydrogenation in the same manner as in Working Example 10 to give 1-[(1R,2R)-2-(2-fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(2H-2-tetrazolyl)phenyl]-2-imidazolidinone (Compound 41) as a colorless crystalline powder.

$^1H$ -NMR ( $CDCl_3$ ) $\delta$ : 1.08 (3H,d,J=7Hz), 3.74-3.81 (1H,m), 3.94-4.13 (3H,m), 4.53 (1H,d,J=14Hz), 4.63-4.81 (1H,m), 5.13 (1H,d,J=14Hz), 5.15-5.30 (1H,br), 6.97-7.07 (2H,m), 7.17-7.45 (2H,m), 7.78 (1H,s), 7.79 (2H,d,J=9Hz), 7.83 (1H,s), 8.13 (2H,d,J=9Hz), 8.65 (1H,s)

Elemental analysis for  $C_{22}H_{22}FN_9O_2$

Calcd (%): C, 57.01; H, 4.78; N, 27.20

Found (%): C, 56.96; H, 4.86; N, 26.84

#### Working Example 42

72% sodium hydride in oil (17 mg) was dispersed in



dimethylformamide (3 ml), to which 1,2,4-triazole (42 mg) was added at ice-bath temperature, and the mixture was stirred at room temperature for 40 minutes. To the resultant was added a solution of 1-[(1R, 2S)-2-(2,4-difluorophenyl)-2,3-epoxy-1-methylpropyl]-3-[4-[(1H-1-tetrazolyl)phenyl]-2H(1H,3H)-imidazolone (0.205 g) in dimethylformamide (2 ml), and the mixture was heated at 50°C for 6 hours. After the mixture was cooled, cold water (30 ml) and ethyl acetate (30 ml) were added thereto. The separated aqueous layer was extracted with ethyl acetate twice. The combined ethyl acetate layers were washed with water and a saturated aqueous solution of sodium chloride successively, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: ethyl acetate) to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (Compound 42; 0.15g) as a colorless crystalline powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.21 (3H,d,J=7Hz), 4.22 (1H,d,J=14Hz), 5.03 (1H,q,J=7Hz), 5.13 (1H,d,J=14Hz), 5.45 (1H,br), 6.74-6.88 (4H,m), 7.42-7.55 (1H,m), 7.77 (1H,s), 7.82 (2H,d,J=9Hz), 7.86 (1H,s), 7.96 (2H,d,J=9Hz), 9.06 (1H,s)

The same product (Compound 42) was obtained when a reaction was carried out in the same manner as in the above except that sodium hydride was replaced by potassium carbon-

ate.

Working Example 43

1-[(1R,2R)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (compound 42) obtained in Working Example 42 was subjected to catalytic hydrogenation in the same manner as in Working Example 10 to give 1-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2-imidazolidinone (compound 43) as a colorless crystalline powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.08 (3H,d,J=7Hz), 3.69-4.14 (4H,m), 4.52 (1H,d,J=14Hz), 4.65-4.80 (1H,m), 5.12 (1H,d,J=14Hz), 5.35 (1H,br), 6.74-6.84 (2H,m), 7.36-7.49 (1H,m), 7.68 (2H,d,J=9Hz), 7.77 (1H,s), 7.82 (2H,d,J=9Hz), 7.87 (1H,s), 8.98 (1H,s)

Working Example 44

72% sodium hydride in oil (120 mg) was dispersed in dimethylformamide (10 ml), to which 1,2,4-triazole (290 mg) was added at ice-bath temperature, and the mixture was stirred at room temperature for 30 minutes. To the resultant was added a solution of 1-[(1R, 2S)-2-(2-fluorophenyl)-2,3-epoxy-1-methylpropyl]-3-[4-[(1H-1-tetrazolyl)phenyl]-2H(1H,3H)-imidazolone (0.82 g) in dimethylformamide (5 ml), and the mixture was heated at 50°C for 5 hours. After the reaction solution was cooled, cold water (30 ml) and ethyl

acetate (40 ml) were added. The separated aqueous layer was extracted with ethyl acetate twice. The ethyl acetate layers were combined, washed with water and a saturated aqueous solution of sodium chloride successively, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: ethyl acetate) to give 1-[(1R,2R)-2-(2-fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (Compound 44; 0.30 g) as a colorless crystalline powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.21 (3H,d,J=7Hz), 4.22 (1H,d,J=14Hz), 5.10 (1H,q,J=7Hz), 5.18 (1H,d,J=14Hz), 5.31 (1H,br), 6.75 (1H,d,J=3Hz), 6.90 (1H,d,J=3Hz), 6.99-7.32 (3H,m), 7.43-7.51 (1H,m), 7.75 (1H,s), 7.80-7.85 (3H,m), 7.97 (2H,d,J=9Hz), 9.07 (1H,s)

#### Working Example 45

1-[(1R,2R)-2-(2-Fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (compound 44) obtained in Working Example 44 was subjected to catalytic hydrogenation in the same manner as in Working Example 10 to give 1-[(1R,2R)-2-(2-fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2-imidazolidinone (Compound 45).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.08 (3H,d,J=7Hz), 3.70-4.19 (4H,m), 4.53

(1H,d,J=14Hz), 4.72-4.88 (1H,m), 5.10-5.26 (2H,m), 6.97-7.45 (4H,m), 7.68 (2H,d,J=9Hz), 7.76 (1H,s), 7.82 (1H,s), 7.83 (2H,d,J=9Hz), 8.97 (1H,s)

Working Example 46

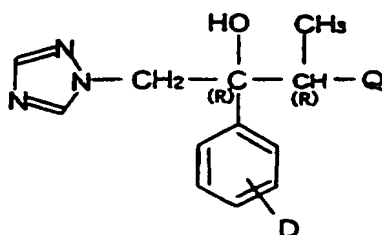
1-[(1R,2S)-2-(2-Fluorophenyl)-2-hydroxy-3-methanesulfonyloxy-1-methylpropyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (200 mg) was dissolved in dimethylformamide (10 ml), to which 1H-1,2,4-triazole (83 mg) and potassium carbonate (168 mg) were added, and the mixture was heated at 50°C for 20 hours. The reaction solution was diluted with ethyl acetate (30 ml), washed with water (15 ml), 1N-hydrochloric acid (15 ml x 2) and a saturated aqueous solution of sodium chloride (15 ml). The organic layer was dried over magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel chromatography (eluent: ethyl acetate). The desired fraction was concentrated and recrystallized from a mixture of ethyl acetate and diisopropyl ether to give 1-[(1R,2R)-2-(2-fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1-tetrazolyl)phenyl]-2(1H,3H)-imidazolone (Compound 44, 65 mg) as a colorless crystalline powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.21 (3H,d,J=7Hz), 4.22 (1H,d,J=14Hz), 5.11 (1H,q,J=7Hz), 5.18 (1H,d,J=14Hz), 5.32 (1H,br), 6.75 (1H,d,J=3Hz), 6.90 (1H,d,J=3Hz), 7.00-7.27 (3H,m), 7.43-7.51

(1H,m), 7.75 (1H,s), 7.80-7.84 (3H,m), 7.97 (2H,d,J=9Hz),  
9.06 (1H,s)

Tables 10 to 14 show a group of preferred compounds  
belonging to the compound (I) of the present invention but  
the present invention is not limited to those compounds.

Table 10



Compound No.	D	Q
<u>1</u>	2,4-F <sub>2</sub>	
<u>2</u>	2,4-F <sub>2</sub>	
<u>3</u>	2,4-F <sub>2</sub>	
<u>4</u>	2,4-F <sub>2</sub>	
<u>5</u>	2,4-F <sub>2</sub>	
<u>6</u>	2,4-F <sub>2</sub>	
<u>7</u>	2,4-F <sub>2</sub>	
<u>8</u>	2,4-F <sub>2</sub>	
<u>9</u>	2,4-F <sub>2</sub>	
<u>10</u>	2,4-F <sub>2</sub>	

Table 11

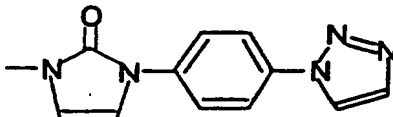
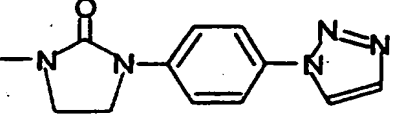
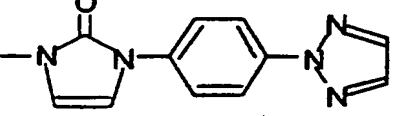
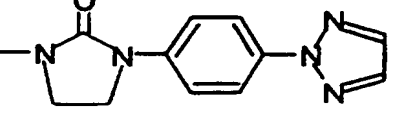
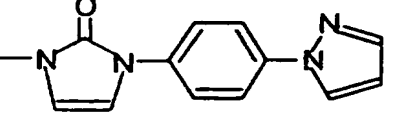
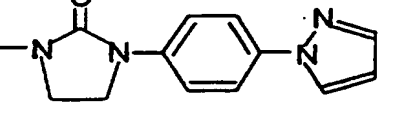
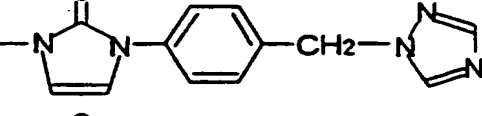
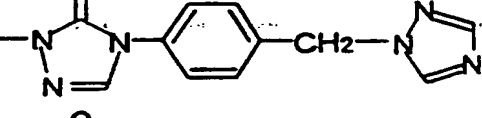
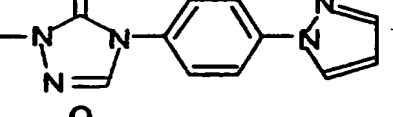
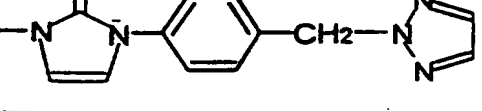
Compound No.	D	Q
<u>11</u>	2,4-F <sub>2</sub>	
<u>12</u>	2,4-F <sub>2</sub>	
<u>13</u>	2,4-F <sub>2</sub>	
<u>14</u>	2,4-F <sub>2</sub>	
<u>15</u>	2,4-F <sub>2</sub>	
<u>16</u>	2,4-F <sub>2</sub>	
<u>17</u>	2,4-F <sub>2</sub>	
<u>18</u>	2,4-F <sub>2</sub>	
<u>19</u>	2,4-F <sub>2</sub>	
<u>20</u>	2,4-F <sub>2</sub>	

Table 12

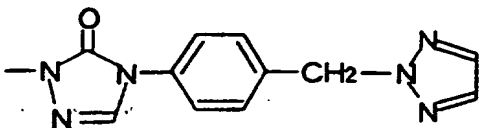
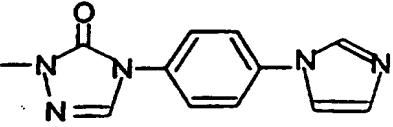
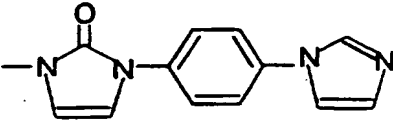
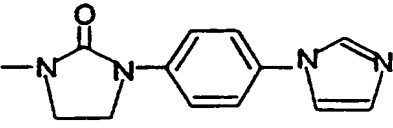
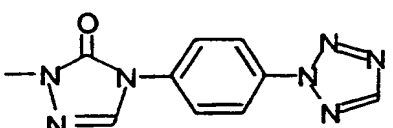
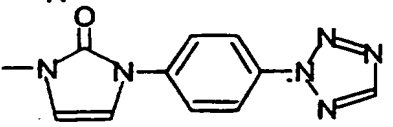
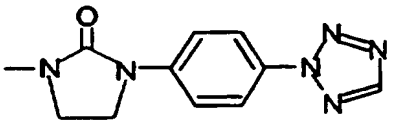
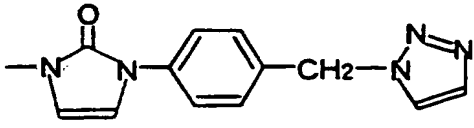
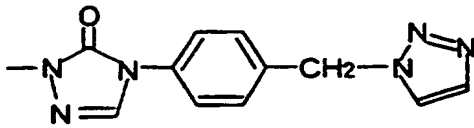
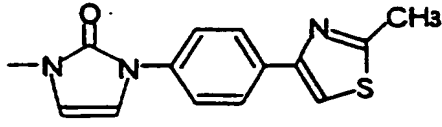
Compound No.	D	Q
<u>21</u>	2,4-F <sub>2</sub>	
<u>22</u>	2,4-F <sub>2</sub>	
<u>23</u>	2,4-F <sub>2</sub>	
<u>24</u>	2,4-F <sub>2</sub>	
<u>25</u>	2,4-F <sub>2</sub>	
<u>26</u>	2,4-F <sub>2</sub>	
<u>27</u>	2,4-F <sub>2</sub>	
<u>28</u>	2,4-F <sub>2</sub>	
<u>29</u>	2,4-F <sub>2</sub>	
<u>30</u>	2,4-F <sub>2</sub>	



Table 13

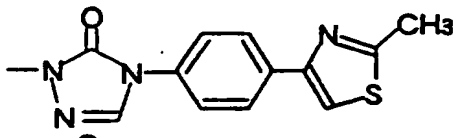
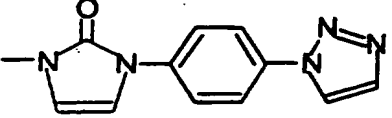
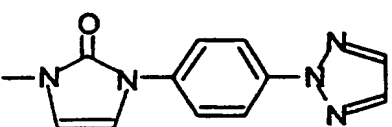
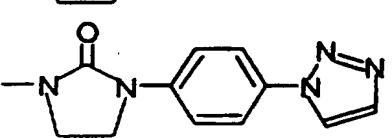
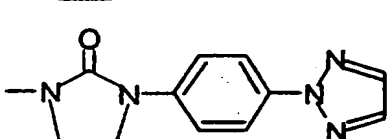
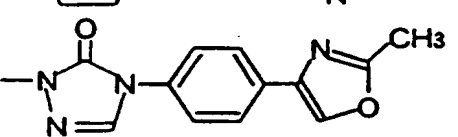
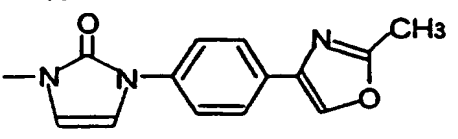
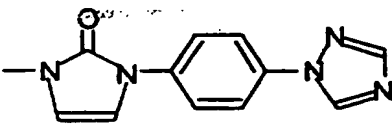
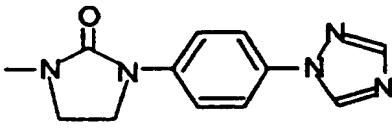
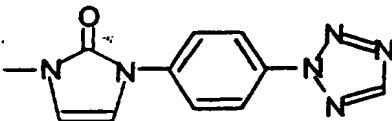
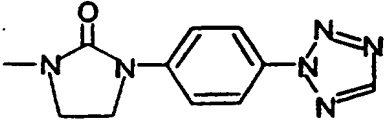
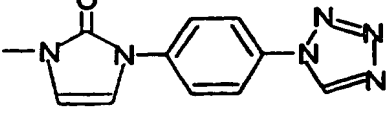
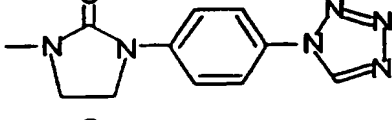
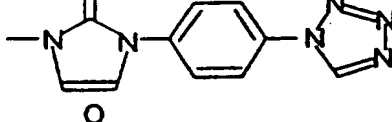
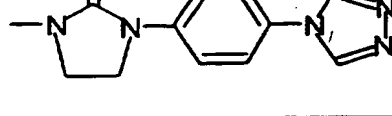
Compound No.	D	Q
<u>31</u>	2,4-F <sub>2</sub>	
<u>32</u>	2-F	
<u>33</u>	2-F	
<u>34</u>	2-F	
<u>35</u>	2-F	
<u>36</u>	2,4-F <sub>2</sub>	
<u>37</u>	2,4-F <sub>2</sub>	
<u>38</u>	2-F	
<u>39</u>	2-F	

Table 14

Compound No.	D	Q
<u>40</u>	2-F	
<u>41</u>	2-F	
<u>42</u>	2,4-F <sub>2</sub>	
<u>43</u>	2,4-F <sub>2</sub>	
<u>44</u>	2-F	
<u>45</u>	2-F	

Formulation Example 1

All the components for the below prescription using the Compound 7 obtained in Working Example 7 were mixed, and filled into gelatine capsules to prepare capsuled drugs each containing Compound 7 in the amount of 50 mg.

Compound <u>7</u> in Working Example 7	50 mg
Lactose	100 mg
Corn Starch	40 mg
Magnesium Stearate	10 mg
Total	200 mg

#### Formulation Example 2

The compound 10 obtained in Working Example 10 and magnesium stearate were made into granules by using an aqueous solution of soluble starch, dried and mixed with lactose and corn starch. The mixture was molded under compression to form a tablet for the below prescription.

Compound <u>10</u> of Working Example 10	50 mg
Lactose	65 mg
Corn Starch	30 mg
Soluble Starch	35 mg
Magnesium Stearate	20 mg
Total	200 mg

#### Experiment Example 1

Test Method: Five-week-old Crj: CDF<sub>1</sub> mice were inoculated with the minimum lethal dose of *Candida albicans* TA intravenously. The test compounds were administered orally once immediately after infection as a 30% HPCD (hydroxypropyl- $\beta$ -cyclodextrin) solution. The activity was expressed in terms of ED<sub>50</sub> value calculated by the Reed and Muench method from the survival rate 7 days after infection.

Result: Tables 15 and 16 shows the protective effects of the

present compounds against *Candida albicans* infection in mice.

Table 15

Compound No .	ED <sub>50</sub> (mg/kg) PO
<u>5</u>	0.22
<u>6</u>	0.35
<u>7</u>	0.096
<u>9</u>	0.16
<u>10</u>	0.32
<u>11</u>	0.45
<u>12</u>	0.71
<u>13</u>	0.18
<u>14</u>	0.32
<u>19</u>	0.39
<u>25</u>	0.088
<u>26</u>	0.16
<u>27</u>	0.18
<u>34</u>	0.80
<u>35</u>	0.71

PO: oral administration

Table 16

Compound No.	ED <sub>50</sub> (mg/kg) PO
<u>38</u>	0.5
<u>39</u>	0.5
<u>40</u>	0.35
<u>41</u>	0.80
<u>42</u>	0.22
<u>43</u>	0.89
<u>44</u>	0.39
<u>45</u>	0.45

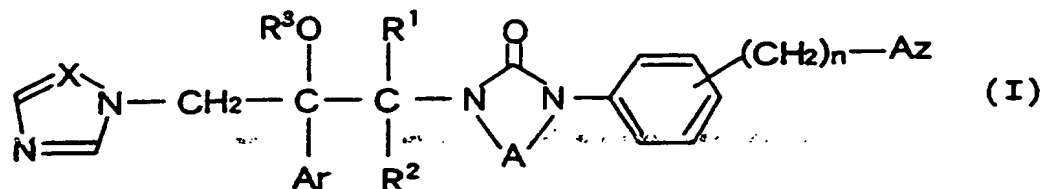
PO: oral administration

## INDUSTRIAL APPLICABILITY

The present compounds or their salts have low toxicity and excellent antifungal activity. Therefore, they are useful in protection and treatment for fungal infections of mammals as antifungal preparations. In addition, they can serve as antifungal preparations for agricultural use.

## CLAIMS

1. A compound represented by the formula (I):



wherein Ar is an optionally substituted phenyl group;  $R^1$  and  $R^2$ , the same or different, are a hydrogen atom or a lower alkyl group, or  $R^1$  and  $R^2$  may combine together to form a lower alkylene group;  $R^3$  is a hydrogen atom or an acyl group; X is a nitrogen atom or a methine group; A is Y=Z (Y and Z, the same or different, are a nitrogen atom or a methine group optionally substituted with a lower alkyl group) or an ethylene group optionally substituted with a lower alkyl group; n is an integer from 0 to 2; and Az is an optionally substituted azolyl group, or a salt thereof.

2. A compound of claim 1 in which Ar is a phenyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a  $C_{1-4}$  haloalkyl group, a  $C_{1-4}$  haloalkoxy group, a  $C_{1-4}$  alkylsulfonyl group and a  $C_{1-4}$  haloalkylsulfonyl group;  $R^1$  and  $R^2$ , the same or different, are a hydrogen atom or a  $C_{1-4}$  alkyl group, or  $R^1$  and  $R^2$  may combine together to form a  $C_{2-4}$

alkylene group;  $R^3$  is a hydrogen atom, a  $C_{1-7}$  alkanoyl group, a  $C_{7-15}$  arylcarbonyl group, a  $C_{2-7}$  alkoxy carbonyl group, a  $C_{7-15}$  aryloxy carbonyl group or a  $C_{8-20}$  aralkyl carbonyl group; A is  $Y=Z$  (Y and Z, the same or different, are a nitrogen atom or a methine group optionally substituted with a  $C_{1-4}$  alkyl group) or an ethylene group optionally substituted with a  $C_{1-4}$  alkyl group; and Az is an azolyl group optionally substituted with one or two substituents selected from the group consisting of an oxo group, a hydroxyl group, a carboxyl group, an optionally esterified carboxyl group, a nitro group, an amino group, a  $C_{1-10}$  alkanoyl amino group, a mono- $C_{1-10}$  alkylamino group, a di- $C_{1-10}$  alkylamino group, a  $C_{1-6}$  alkyl group, a  $C_{1-6}$  alkoxy group, a halogen atom, a  $C_{1-6}$  haloalkyl group, a  $C_{1-6}$  haloalkoxy group, a thioxo group, a mercapto group, a  $C_{1-6}$  alkylthio group, a  $C_{1-6}$  alkylsulfonyl group, a  $C_{1-10}$  alkanoyl group, a phenyl group, a  $C_{1-6}$  alkylphenyl group, a  $C_{1-6}$  alkoxyphenyl group, a halophenyl group, a  $C_{1-6}$  haloalkylphenyl group and a  $C_{1-6}$  haloalkoxyphenyl group.

3. A compound of claim 1 in which an azolyl group of Az is a five-membered aromatic heterocyclic group which contains one to four nitrogen atoms as ring-constituent atom(s) and may further contain a sulfur or oxygen atom as a ring-constituent atom.

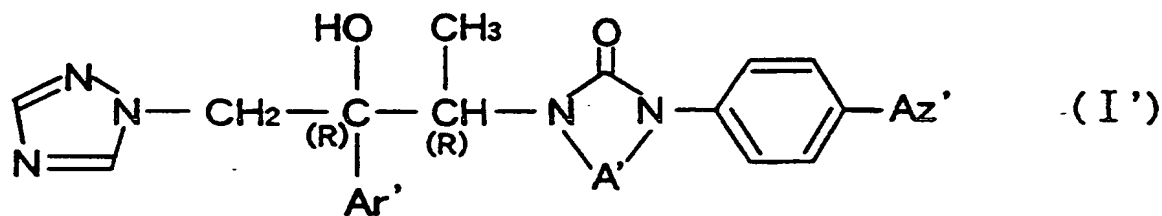


4. A compound of claim 1 in which one of  $R^1$  and  $R^2$  is a hydrogen atom and the other is a  $C_{1-4}$  alkyl group.
5. A compound of claim 4 in which the carbon atom to which Ar is bonded is an (R)-configuration and the carbon atom to which  $R^2$  is bonded is an (R)-configuration.
6. A compound of claim 1 in which  $R^3$  is a hydrogen atom.
7. A compound of claim 1 in which X is a nitrogen atom.
8. A compound of claim 1 in which Ar is a halophenyl group.
9. A compound of claim 8 in which Ar is a phenyl group substituted with one or two fluorine atoms.
10. A compound of claim 9 in which Ar is a 2-fluorophenyl group or a 2,4-difluorophenyl group.
11. A compound of claim 1 in which A is  $-CH_2-CH_2-$ .
12. A compound of claim 1 in which A is  $-N=CH-$ ,  $-CH=N-$  or  $-CH=CH-$ .
13. A compound of claim 1 in which n is 0.
14. A compound of claim 1 in which Az is a diazoly, triazoly, tetrazoly, thiazoly or oxazoly group, which is optionally substituted with one or two substituents selected from the group consisting of an oxo group, a  $C_{1-6}$  alkyl

group, a C<sub>1-6</sub> haloalkyl group and a C<sub>1-6</sub> haloalkyloxy-phenyl group.

15. A compound of claim 1 in which Az is a triazolyl group or a tetrazolyl group.

16. A compound of claim 1 which is represented by the formula (I'):



wherein Ar' is a monofluorophenyl or difluorophenyl group; A' is -N=CH-, -CH=CH- or -CH<sub>2</sub>-CH<sub>2</sub>-; and Az' is a diazolyl, triazolyl, tetrazolyl, thiazolyl or oxazolyl group which is optionally substituted with one or two substituents selected from the group consisting of an oxo group, a C<sub>1-6</sub> alkyl group, a C<sub>1-6</sub> haloalkyl group and a C<sub>1-6</sub> haloalkyloxyphenyl group, or a salt thereof.

17. A compound of claim 16 in which A' is -CH<sub>2</sub>-CH<sub>2</sub>-; and Az' is triazolyl group or a tetrazolyl group.

18. A compound of claim 1 which is 1-[(1R, 2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,4-triazol-1-yl)phenyl]-2-

imidazolidinone or a salt thereof.

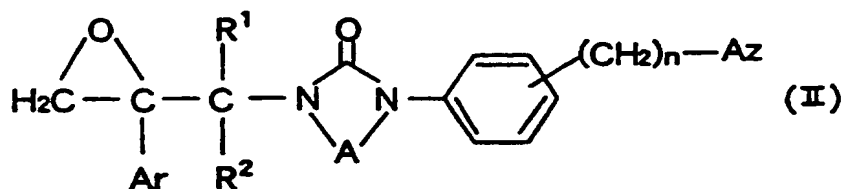
19. A compound of claim 1 which is 1-[(1R, 2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(1H-1,2,3-triazol-1-yl)phenyl]-2-imidazolidinone or a salt thereof.

20. A compound of claim 1 which is 1-[(1R, 2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-3-[4-(2H-2-tetrazolyl)phenyl]-2-imidazolidinone or a salt thereof.

21. A process for preparing a compound of the formula (I) as defined in claim 1 or a salt thereof which comprises

(1) reacting a compound represented by the formula

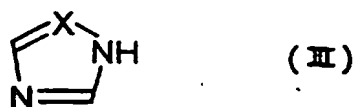
(II):



wherein Ar is an optionally substituted phenyl group;  $R^1$  and  $R^2$ , the same or different, are a hydrogen atom or a lower alkyl group, or  $R^1$  and  $R^2$  may combine together to form a lower alkylene group; A is Y=Z (Y and Z, the same or different, are a nitrogen atom or a methine group optionally substituted with a lower alkyl group) or an ethylene group optionally substituted with a lower alkyl group; n is an

integer from 0 to 2; and Az is an optionally substituted azolyl group; or a salt thereof,

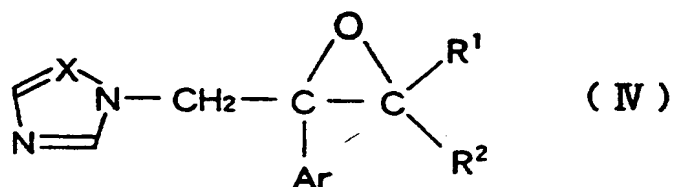
with a compound represented by the formula (III):



wherein X is a nitrogen atom or a methine group, or a salt thereof, and, optionally followed by an acylation if R<sup>3</sup> is not hydrogen;

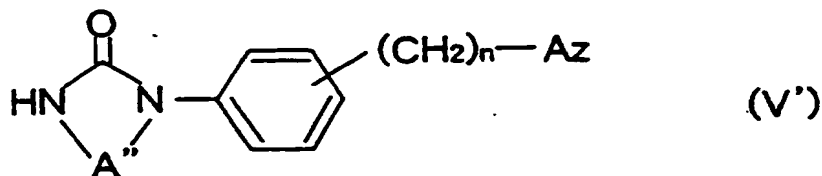
(2) reacting a compound represented by the formula

(IV):



wherein Ar is an optionally substituted phenyl group; R<sup>1</sup> and R<sup>2</sup>, the same or different, are a hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> may combine together to form a lower alkylene group; and X is a nitrogen atom or a methine group; or a salt thereof,

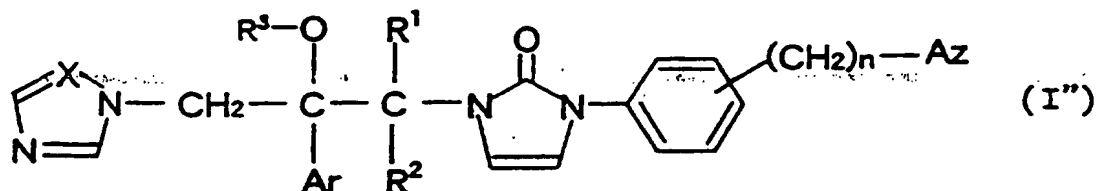
with a compound represented by the formula (V'):



wherein A'' is -N=CH-, -CH=N- or -CH=CH-; n is an integer from 0 to 2; and Az is an optionally substituted azolyl

group; or a salt thereof, and, optionally followed by an acylation if  $R^3$  is not hydrogen; or

(3) reducing a compound represented by the formula (I'')



wherein Ar is an optionally substituted phenyl group;  $R^1$  and  $R^2$ , the same or different, are a hydrogen atom or a lower alkyl group, or  $R^1$  and  $R^2$  may combine together to form a lower alkylene group;  $R^3$  is a hydrogen atom or an acyl group; X is a nitrogen atom or a methine group; n is an integer from 0 to 2; and Az is an optionally substituted azolyl group, or a salt thereof, and, optionally followed by an acylation if  $R^3$  is not hydrogen.

22. A pharmaceutical composition which comprises a pharmacologically effective amount of a compound of the formula (I) as defined in claim 1 or its pharmaceutically acceptable salt and one or more of a carrier and diluent.

23. A method for a prevention or treatment of a fungal infection which comprises administration of a pharmacologically effective amount of a compound of the formula (I) as defined in claim 1 or its pharmaceutically acceptable salt.

24. Use of a compound of the formula (I) as defined in

claim 1 or pharmaceutically acceptable salt thereof, as an active ingredient for the preparation of an antifungal agent which comprises the compound of the formula (I) or a salt thereof.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 96/00325

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D403/14 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 567 982 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 3 November 1993 cited in the application see claims ---	1-24
A	EP,A,0 548 553 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 30 June 1993 see claims ---	1-24
P,A	EP,A,0 657 449 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 14 June 1995 see claims -----	1-24

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*A\* document member of the same patent family

Date of the actual completion of the international search

15 April 1996

Date of mailing of the international search report

26. 04. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+ 31-70) 340-3016

Authorized officer

Chouly, J

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 96/00325

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-567982	03-11-93	AU-B- 3822193	04-11-93
		CA-A- 2094962	29-10-93
		CN-A- 1079467	15-12-93
		HU-A- 64327	28-12-93
		JP-A- 6293740	21-10-94
		NZ-A- 247488	24-02-95
		US-A- 5371101	06-12-94
		US-A- 5466820	14-11-95
		ZA-A- 9302991	08-11-93
EP-A-548553	30-06-93	AU-B- 653082	15-09-94
		AU-B- 2859292	31-03-94
		CN-A- 1075143	11-08-93
		FI-A- 925323	26-05-93
		JP-A- 6049033	22-02-94
		NZ-A- 245226	26-10-94
		US-A- 5495024	27-02-96
		US-A- 5371100	06-12-94
		ZA-A- 9209146	25-05-94
EP-A-657449	14-06-95	AU-B- 7299694	06-04-95
		CA-A- 2132791	25-03-95
		CN-A- 1106390	09-08-95
		FI-A- 944417	25-03-95
		HU-A- 71333	28-11-95
		NO-A- 943510	27-03-95
		NZ-A- 264519	26-09-95